

**8th Annual Report of the  
National Institutes of Health**

**PROGRAM IN BIOMEDICAL  
AND BEHAVIORAL NUTRITION  
RESEARCH AND TRAINING  
FISCAL YEAR 1984**



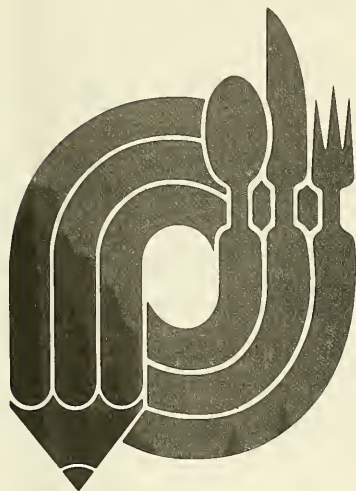
**NIH Nutrition  
Coordinating Committee**

**U.S. DEPARTMENT OF  
HEALTH AND HUMAN SERVICES  
Public Health Service  
National Institutes of Health**



8th Annual Report of the  
National Institutes of Health (U. S.)  
"

# **PROGRAM IN BIOMEDICAL AND BEHAVIORAL NUTRITION RESEARCH AND TRAINING FISCAL YEAR 1984**



Prepared by  
NIH Nutrition  
Coordinating Committee

U.S. DEPARTMENT OF  
HEALTH AND HUMAN SERVICES  
Public Health Service  
National Institutes of Health

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As of September 30, 1984

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Division of Computer Research and Technology	Diane Feskanich (Arnold Pratt, M.D.)
Division of Research Grants	John Schubert, Ph.D. (Julius A. Currie, Ph.D.)
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Cochairperson and Executive Secretary	Karen Donato, M.S., R.D. Nutrition Coordinating Committee Office
Special Consultant	Nancy Ernst, M.S., R.D. National Heart, Lung, and Blood Institute

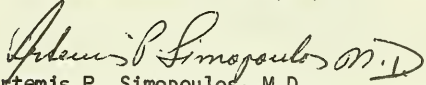
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National Eye Institute	Barbara Underwood, Ph.D.
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I want to pay special thanks to the Institutes' representatives to the Nutrition Coordinating Committee whose unfaltering support and interest in nutrition research has made possible the development of the report. On behalf of the Nutrition Coordinating Committee I wish to thank three members of the NCC office staff: Ms. Karen Donato for her excellent work in updating the annual report; Dr. Thomas Vogl for the extensive analysis of the program based on the computerized data retrieval system; and Ms. Sherri Wisner for her editorial and technical assistance in the preparation of the report.

  
Artemis P. Simopoulos, M.D.  
Chairman, Nutrition Coordinating Committee  
Office of the Director  
National Institutes of Health



## INTRODUCTION

The National Institutes of Health (NIH) is the major agency in the Federal Government that supports research and training in nutrition as it relates to health maintenance, human development throughout the life cycle, disease prevention, and disease treatment. The NIH Program in Biomedical and Behavioral Nutrition Research and Training is supported by all 11 Institutes, the Division of Research Resources and the Fogarty International Center (FIC).

Nutrition is an important, crosscutting program area within the NIH. For this reason, the nutrition program is coordinated through the NIH Nutrition Coordinating Committee (NCC) that operates out of the Office of the Director and is advisory to the Director. Each year, the NCC prepares the Annual Report of the NIH Program in Biomedical and Behavioral Nutrition Research and Training for the preceding fiscal year and sponsors a major conference or workshop in nutrition that includes the interests of many Institutes.

The FY 1984 Report of the NIH Program in Biomedical and Behavioral Nutrition Research and Training is the eighth annual report prepared by the NCC and differs significantly from all previous reports, both in content and format, with 7 major parts and 11 appendices. For the first time, the report begins with a new section entitled "Trends in Nutrition Research and Research Training." In addition, three areas of the nutrition research program, i.e., "Nutrition and Prevention of Disease," "Nutritional Status Assessment," and "Epidemiological Research in Nutrition," are highlighted in the report and described in detail in the appendices because of their scientific and political interest. The report also highlights the studies supported by the various Institutes that relate to the Initial Followup of the National Health and Nutrition Examination Surveys: NHANES I Followup and NHANES II.

Part I, "Trends in Nutrition Research and Research Training," features the impact of legislative activities on the development of definition of nutrition research and the coordination of nutrition research at the Federal level, followed by an historical perspective on the nutrition research and training program and funding trends from FY 1977 to FY 1984. Part I closes with a list of reports published by the NCC office.

Part II of the report, "Highlights of the Nutrition Research Program and Program Development," begins with nutrition research highlights of particular scientific interest and importance. This year's highlights feature studies on infant nutrition and composition of human milk, nutrition and behavior, food allergy, coronary heart disease, nutrition and aging, osteoporosis, etc. In terms of program development in nutrition, 47 new PA's, RFA's, and RFP's developed and published by the Institutes, as well as jointly through the NCC are listed. One particularly important announcement, the Joint PA "Core Grants for Clinical Nutrition Research Units" was revised and reissued by NIADDK, NCI and NIA in August 1984 in order to encourage the establishment of additional Clinical Nutrition Research Units (CNRU).

Concluding part II is a description of the CNRU program, and a list of the 14 nutrition conferences sponsored by the Institutes and the NCC in FY 1984.

Part III, "FY 1984 Obligations for Nutrition Research and Training," describes the data retrieval system/Human Nutrition Research and Information Management System used by the NCC for the analysis of the nutrition program, both in terms of fiscal data and narrative research summaries. Included in this year's analysis is an overview of the entire nutrition research program; i.e., its distribution by the percentage of the nutrition component, by support mechanisms, by the 34 HNRIM classification categories and 6 special interest areas, and by extramural and intramural nutrition research and research training. Actual obligations for nutrition are compared with NIH obligations as a whole for three major components of extramural research, and for research training as well as fellowships.

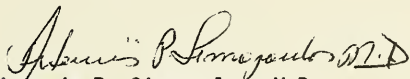
Part IV of the report, "Coordination of Nutrition Research at the NIH," presents the structure and mandate of the NCC, as well as the charges of its two subcommittees, the Program Subcommittee and Subcommittee on Nutrition Education. The Nutrition Policy of the NIH and the Definition of Nutrition Research, developed by the NCC in FY 1977, are also included in this section of the report. The role of the NCC office in coordinating the many aspects of nutrition research at the NIH is highlighted.

Part V presents highlights of the activities and accomplishments of the NCC, the Program Subcommittee, and the Subcommittee on Nutrition Education in FY 1984. One activity of ongoing interest to the NCC is the "Eat Well, Be Well" videotape series. In FY 1984, "Eat Well, Be Well II," produced by Amram Nowak Associates with funds from the Metropolitan Life Insurance Foundation in consultation with the NCC, was shown at a number of scientific and organizational meetings and health fairs. Plans are under way for the production of "Eat Well, Be Well III" and publication of the "Eat Well, Be Well Cookbook" in FY 1985. Highlights of the two nutrition conferences cosponsored by the NCC, i.e., the "Outpatient Management of Obesity," and the "NIH Workshop on Nutrition and Hypertension" are presented. The Program Subcommittee's activities include the development and publication of the second joint PA in nutrition with ADAMHA, entitled "Studies on Obesity." Another particularly exciting and timely activity involved the participation of the subcommittee members in the planning meeting for the joint conference on the "Health Effects of Polyunsaturated Fatty Acids in Seafoods," scheduled for June 24-26, 1985, and cosponsored by the NCC; the National Marine Fisheries Service, National Oceanic and Atmospheric Administration, Department of Commerce; and the National Fisheries Institute. The Subcommittee on Nutrition Education reviewed seven NIH nutrition publications intended for the public and, for the fourth consecutive year, was instrumental in the implementation of National Nutrition Month Activities at the NIH. The NIH-NCC Nutrition Research Exhibit, developed by the subcommittee and the NCC in FY 1983, was displayed and enthusiastically received at four major scientific meetings and numerous health fairs.

Part VI describes the major responsibilities and activities of the NCC office. These activities encompass: responding to information requests about nutrition in general and about the NIH nutrition program in particular from the Congress, other Federal agencies, the scientific community and the public; representing NIH in various nutrition activities under way at the Office of the Assistant Secretary for Health; and presenting the NIH Program in Nutrition at national and international meetings, conferences, and workshops. The development of the Federal Human Nutrition Research and Information Management System is presented, followed by highlights of the work accomplished through the Departmental Research Initiative in Nutrition and the Interagency Committee on Human Nutrition Research.

Part VII consists of 11 appendices: appendix A presents the HNRIM classification system and the FY 1984 expenditures by HNRIM category and special interest area; appendix B presents the FY 1984 nutrition expenditures of the 11 Institutes, DRR, and FIC by support mechanism; and appendix C includes the descriptions of the extramural and intramural nutrition research and research training programs by Institute. Appendices D, E and F include detailed descriptions of "Research on Nutrition and Prevention of Disease," "Research on Nutritional Status Assessment," and "Epidemiological Research in Nutrition." Appendix G presents the studies related to the National Health and Nutrition Examination Surveys: NHANES I Followup and NHANES II; appendix H describes the 47 PA's, RFA's and RFP's; appendix I includes the summaries of the NCC scientific seminars; appendix J lists the "Guidelines for the Review of NIH Nutrition Publications Intended for the Public," and appendix K includes the legislative authority of NIH for human nutrition research.

Over the years, requests for the annual reports have come from members of the scientific community, Congress, professional societies, libraries, and interested consumers. The NCC office is pleased with the interest shown in the activities of the NCC on the part of scientists and governments, nationally and internationally. Interest in nutrition research is indeed universal. In order to satisfy the interests and needs of such an ecumenical audience, this year's report is arranged in such a way that the largest part of the report is made up of 11 appendices with detailed descriptions for the interested reader.



Artemis P. Simopoulos, M.D.  
Chairman,  
Nutrition Coordinating Committee  
Office of the Director, NIH





I.

**TRENDS IN NUTRITION  
RESEARCH AND RESEARCH  
TRAINING, FY 1977-FY 1984**





TRENDS IN NUTRITION RESEARCH AND RESEARCH TRAINING,  
FY 1977 - FY 1984

Introduction

This year's report on the Program of Biomedical and Behavioral Nutrition Research and Training is the 8th annual report. One octave has been completed; therefore, it is time to include a chapter on the trends in nutrition research of the NIH in this report. When appropriate, reference to the overall efforts of the other agencies and departments of the Federal Government will be made.

In describing trends in nutrition research, the legislative activities that have influenced the development of these trends must be recognized. The most significant of these activities are summarized below.

Legislative Activities

The years 1977 and 1978 were very important for nutrition research. In 1977, the Dietary Goals for the United States was published by the Select Committee on Nutrition and Human Needs, U.S. Senate, and in 1978, two major events, in terms of congressional decisionmaking, took place.

The first event was the September 1978 Conference Report on P.L. 95-448 (C.R. Number 95-1579) "Making Appropriations for the Agriculture, Rural Development, and Related Agencies' Programs" which states:

"The conferees have agreed that the centers at Baylor and Tufts are to be operated by the Science and Education Administration of the Department of Agriculture and be a part of the coordinated nutrition research program conducted by the department. The conferees are concerned that the purpose of the research program at the centers be consistent with the research program of the National Institutes of Health and that the centers support similarly high quality programs."

In response to this mandate, two Cooperative Agreements were executed; the National Institute of Child Health and Human Development, Baylor College of Medicine, Texas Children's Hospital, and USDA signed Cooperative Agreement No. 58-7B30-9-60 regarding the program at the USDA Children's Nutrition Research Center which specifies that a representative of NICHD shall serve on the executive committee of the Center; and the National Institute on Aging, Tufts University, and USDA signed Cooperative Agreement No. 5832U4-9-79, which specifies that a DHHS representative from NIA shall serve on the executive committee of the USDA Center for Research on Human Nutrition and Aging.

The second event was the enactment, on November 9, 1978, of Public Law 95-622, "An Amendment to the Public Health Service [PHS] Act," which states in part:

"The Secretary [of HEW] shall conduct, and may support through grants and contracts, research and studies on human nutrition, with particular emphasis on the role of nutrition in the prevention and treatment of disease and on the maintenance and promotion of health and programs for the dissemination of information respecting human nutrition to health professionals and the public."

These actions, along with a series of hearings on nutrition and health, brought into focus the need for (1) a definition of modern nutrition research and (2) the coordination of nutrition research and training at the Federal level. To answer these needs and to provide a focus within the NIH, the Nutrition Coordinating Committee (NCC) was transferred by Donald S. Fredrickson, M.D., then the Director of NIH, into his Office on May 11, 1977.

Another important piece of legislation was passed three years later. In December 1981, Congress mandated the Secretaries of Agriculture and Health and Human Services to formulate a plan for a Human Nutrition Research and Information Management System. Section 1427 of the National Agricultural Research, Extension and Teaching Policy Act of 1977 (7 U.S.C. 3177), as amended by Section 1425 of the National Agricultural Research, Extension, and Teaching Policy Act Amendments of 1981 (Title XIV of P.L. 97-98) provides as follows:

HUMAN NUTRITION RESEARCH AND INFORMATION MANAGEMENT SYSTEM  
Section 1427. The Secretary [of Agriculture] and the Secretary of Health and Human Services shall formulate and submit to Congress, within one hundred and eighty days after the date of enactment of this section, a plan for a human nutrition research management system. This system shall be based on on-line data support capability allowing for fiscal accounting, management, and control of cross-agency human nutrition research activities. The plan shall provide for management activities of all agencies managing funds for human nutrition research activities under existing authorities and contain recommendations for any additional authorities necessary to achieve a human nutrition research management system.

In response to the legislation, DHHS Secretary Schweiker asked Dr. Artemis P. Simopoulos, the NCC Chairman, to cochair the group to develop the plan together with the USDA counterpart, Dr. Jack Iacono. In July 1982, the Secretaries transmitted the plan to Congress.

The Human Nutrition Research and Information Management (HNRIM) System is a computerized data base and information retrieval system that operates out of the NCC office and contains fiscal and scientific information on human nutrition research and training supported by the following Federal agencies: Agency for International Development; Department of Commerce-National Oceanic and Atmospheric Administration; Department of Defense; Department of Health and Human Services; National Aeronautics and Space Administration; National Science Foundation; United States Department of Agriculture; and the Veterans Administration.



## Coordination of Nutrition Research and Research Training

The primary mission of the NIH is fostering, supporting, and conducting laboratory and clinical research to increase the understanding of life processes and the etiology, treatment, and prevention of diseases. Nutrition is an important, crosscutting program area within the NIH. For this reason, the nutrition program is coordinated through the NIH Nutrition Coordinating Committee (NCC) that operates out of the Office of the Director, and is advisory to the Director. The membership of the NCC consists of representatives from the 11 Institutes, the Division of Research Resources, and Fogarty International Center that support nutrition research. Additional NIH Offices and other agencies of the Department of Health and Human Services have liaison representatives to the committee. Within NIH, nutrition research and training are supported by:

- o National Cancer Institute
- o National Heart, Lung, and Blood Institute
- o National Institute of Dental Research
- o National Institute of Arthritis, Diabetes, and Digestive and Kidney Diseases
- o National Institute of Neurological and Communicative Disorders and Stroke
- o National Institute of Allergy and Infectious Diseases
- o National Institute of General Medical Sciences
- o National Institute of Child Health and Human Development
- o National Eye Institute
- o National Institute of Environmental Health Sciences
- o National Institute on Aging
- o Division of Research Resources
- o Fogarty International Center

The NCC published its first annual report in FY 1977, entitled Report of the National Institutes of Health Program in Biomedical and Behavioral Nutrition Research and Training. Since 1977, the NCC developed:

- o its mandate,
- o the nutrition policy of the NIH,
- o the definition of human nutrition research,
- o the data retrieval system,
- o annual reports on the NIH Program in Biomedical and Behavioral Nutrition Research and Training,
- o the concept of the Clinical Nutrition Research Unit (CNRU),
- o the first joint program announcement in nutrition among NIH Institutes
- o the first joint program announcement in nutrition between NIH and ADAMHA, and

- o guidelines for the review of all NIH nutrition publications destined for the public and public service announcements.

In June 1978, the NCC held a conference on the Scientific Basis of Clinical Nutrition in order to: (1) review the science base of clinical nutrition, and (2) determine directions for future research. The planning committee consisted of officers of the following scientific organizations:

Executive Committee Assembly of Life Sciences, National Research Council, National Academy of Sciences  
American Diabetes Association  
Food and Nutrition Board, National Research Council, National Academy of Sciences  
American Society for Clinical Nutrition  
American Gastroenterology Association  
American Institute of Nutrition  
National Nutrition Consortium

At the conference the definition of nutrition research developed by the NCC as well as the NIH nutrition research program were presented and accepted by the attendees. The conferees made the following recommendations:

1. The NIH should establish a new national program in clinical nutrition through the support and development of Clinical Nutrition Research Units.
2. The NIH should continue to support investigator-initiated nutrition research in areas of particular interest and importance, and should expand its research in clinical nutrition.
3. Concerned NIH Institutes should make a concerted effort to expand training in nutrition research.
4. Current NIH programs in nutrition education for the public and for professionals should be expanded, and new programs should be developed.
5. The coordination of nutrition research programs should be strengthened among the Federal agencies.

All five of these recommendations have been implemented. Cooperation among the Federal agencies began in 1978 with the establishment of the Joint Subcommittee on Human Nutrition Research (JSHNR) under the auspices of the Office of Science and Technology Policy, Executive Office of the President, cochaired by Artemis P. Simopoulos, M.D., Chairman of the NCC, NIH, and D. Mark Hegsted, Ph.D., Administrator, Human Nutrition-SEA, USDA. The NCC Office carried out the responsibilities of the Executive Secretary of the JSHNR until June 1983, when the JSHNR was abolished and succeeded by the Interagency Committee on Human Nutrition Research (ICHNR), cochaired by the Assistant Secretary for Health, DHHS, and the Assistant Secretary for Science and Education, USDA.

## Funding Trends

Within the Federal Government, NIH is the major agency for the support of nutrition research and research training, providing 73 percent of the funds. Table I shows the distribution of expenditures by Federal agency for FY 1984. The total FY 1984 Federal expenditures for nutrition research and training were \$266.3 million, of which NIH accounted for \$192.9 million (73 percent) and USDA for \$53.1 million (20 percent). The NIH nutrition expenditures accounted for 95.5 percent of total DHHS nutrition expenditures.

TABLE I

FY 1984 EXPENDITURES AND NUMBER OF PROJECTS IN HUMAN NUTRITION  
RESEARCH, MANPOWER DEVELOPMENT, TRAINING, AND EDUCATION  
BY FEDERAL AGENCIES  
(dollars in thousands)

	Expenditures		Projects	
	\$	%	Number*	%
Department of Health and Human Services:				
National Institutes of Health	\$192,918	73	2,342	63
Alcohol, Drug Abuse and Mental Health Administration	3,928	1.5	67	2
Food and Drug Administration	4,504	1.5	33	1
Health Resources and Services Administration	298	0	5	0
Centers for Disease Control	259	0	1	0
Total DHHS	201,907	76	2,448	66
U.S. Department of Agriculture	53,051	20	873*	24
Veterans Administration	4,631	2	282	8
Agency for International Development	5,521	2	18	0
Department of Defense	0	0	0	0
National Science Foundation	850*	0	75*	2
Department of Commerce	342	0	5	0
Total Federal Expenditures	\$266,302	100	3,701*	100

\* Estimate

Figure 1 indicates the support of nutrition research and training by all Federal agencies from FY 1979 through FY 1984. The funding trend for all Federal agencies combined is similar to that of NIH alone since NIH is the major supporter of nutrition research and training. The NIH program is largely (93 percent) extramural, while the USDA program is predominantly intramural.

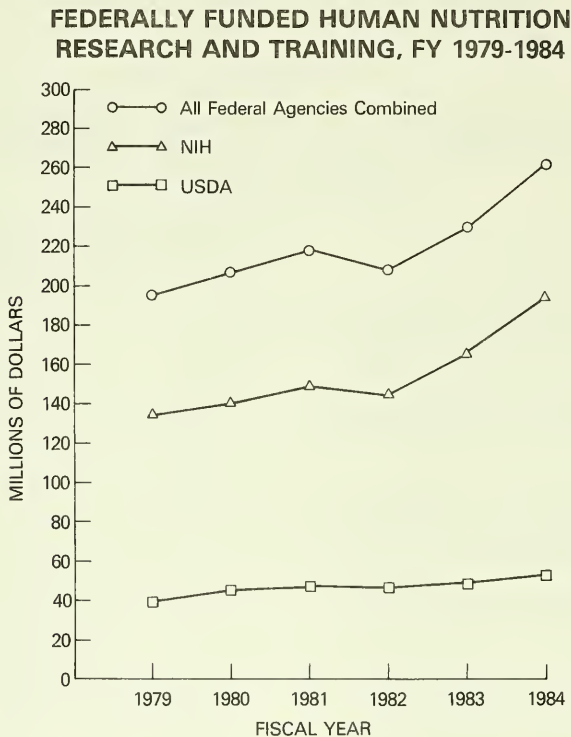


Figure 1

Figure 2 compares NIH and USDA expenditures for FY 1983 (the latest USDA data available) in the following seven groupings:

- I. Research on Normal Nutritional Requirements Throughout the Life Cycle,
- II. Research on the Role of Nutrients in Diseases and Conditions,
- III. Research on Nutrient Metabolism and Mechanisms at the Cellular Level,
- IV. Research in Food Sciences,
- V. Research on Nutrition Monitoring and Surveillance of Populations,
- VI. Research in Nutrition Education, and
- VII. Research on the Effects of Government Policy and Socioeconomic Factors on Food Consumption and Human Nutrition.

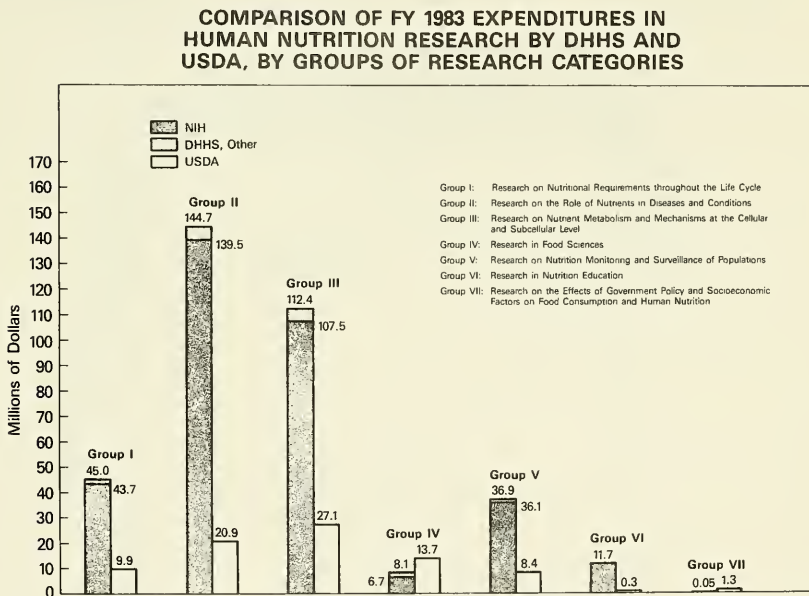


Figure 2

The figure shows that NIH is the predominant supporter of research in five of the seven groups: Research on Normal Nutritional Requirements Throughout the Life Cycle; Research on the Role of Nutrients in

Diseases and Conditions; Research on Nutrient Metabolism and Mechanisms at the Cellular Level; Research on Nutrition Monitoring and Surveillance of Populations; and Research in Nutrition Education. USDA is the predominant supporter of research in two of the groups: Research in Food Sciences and Research on the Effects of Government Policy and Socioeconomic Factors on Food Consumption and Human Nutrition.

Figure 3 shows a comparison of the total NIH appropriations and the NIH expenditures for nutrition research and training from FY 1977 through FY 1984. As can be seen, nutrition research and training continues to increase in parallel to the total NIH budget. In FY 1977, 3.7 percent of the total NIH budget was expended on nutrition research. Since then, the support for nutrition research has expanded by 16 percent to 4.3 percent of the total NIH budget.

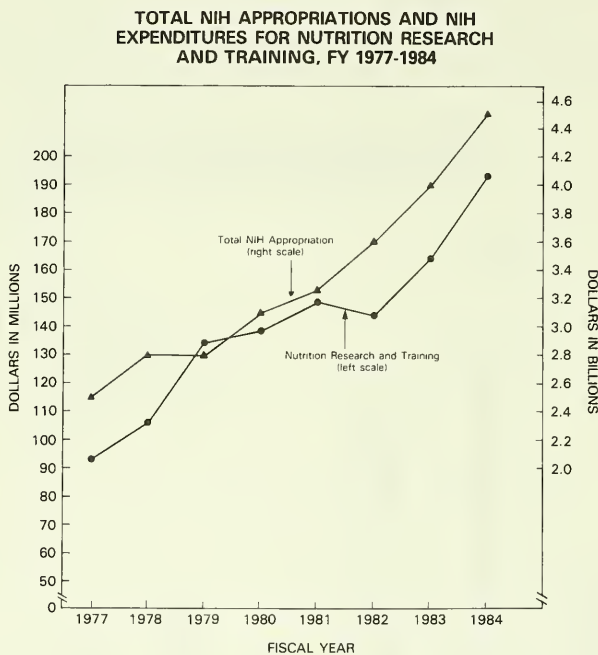


Figure 3

Figure 4 shows trends in NIH expenditures from FY 1977 through FY 1984 in three areas of nutrition research selected for their scientific and political importance: the role of nutrition research in disease prevention, nutritional status, and epidemiological research in nutrition. The largest expenditure of these three has been on the role



of nutrition in the prevention of disease, which, except for 1979, has shown a consistent increase over time. The definitions for prevention used by the NCC for data retrieval are:

Primary prevention. Actions to promote health or undertaken prior to the development of disease; i.e., studies on nutrients to define nutritional requirements for health maintenance.

Secondary prevention. Detection of disease in its early (asymptomatic) stages and intervention to arrest its expression; i.e., the use of a low phenylalanine diet in children with phenylketonuria (PKU) in order to prevent mental retardation.

Tertiary prevention. Intervention after the development of a clinically manifest disease in order to reverse or arrest its progression; i.e., studies on sodium excretion for the treatment of hypertension and on low sodium diets for the treatment of the "salt-sensitive" hypertensive.

Expenditures on nutritional status showed an increase through FY 1981 followed by a sharp drop in FY 1982, and increases in FY 1983 and FY 1984 to about the FY 1981 level. Epidemiological research expenditures have almost tripled since 1977.

**NIH EXPENDITURES IN NUTRITION AND  
DISEASE PREVENTION, RESEARCH ON  
NUTRITIONAL STATUS, AND EPIDEMIOLOGICAL  
RESEARCH IN NUTRITION, FY 1977-1984**

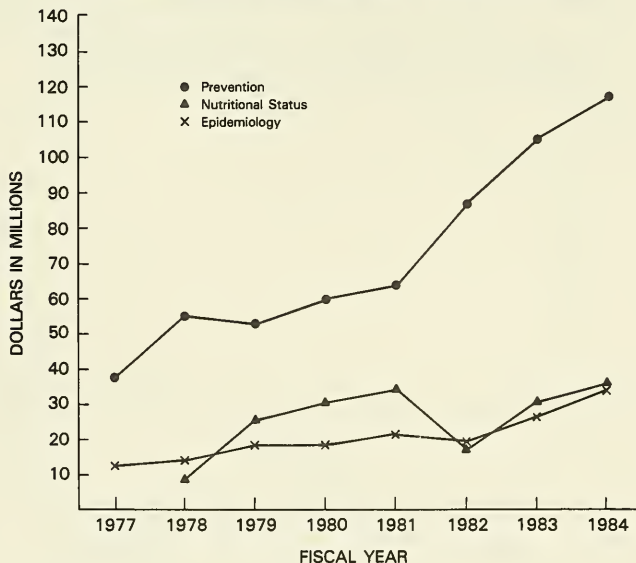


Figure 4

Although authority for research training exists in the legislation of three Federal agencies, DHHS, NSF, and USDA, NIH is the major agency for the support of research training in nutrition. Figure 5 shows the number of persons supported by NIH training grants and fellowships in nutrition from FY 1977 - FY 1984. Despite some oscillations, there has been a consistent upward trend in the number of persons trained. The number of postgraduates receiving training grants and fellowships is greater than the number of undergraduates; scientists with a Ph.D. degree slightly outnumber those with professional degrees in medicine, dentistry, and veterinary medicine.

**NUMBER OF PREDOCTORAL STUDENTS, Ph.Ds,  
AND PERSONS WITH PROFESSIONAL DEGREES  
SUPPORTED BY TRAINING GRANTS AND  
FELLOWSHIPS IN NUTRITION, FY 1977-1984**

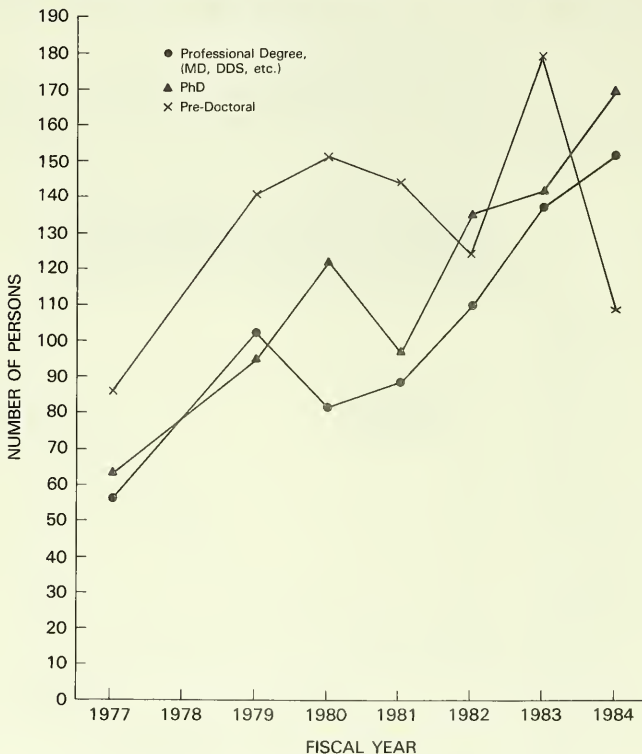


Figure 5



### Trends in Program Development

A major function of the NCC is to actively foster program development in nutrition research and training. The committee is the focus for the review of nutrition research and training priorities, their coordination, and for the development of the NIH Program in Biomedical and Behavioral Nutrition Research and Training. This focus minimizes duplication of effort among the Institutes and identifies areas where research, research training, and research manpower development in nutrition need to be advanced. This is accomplished through joint program announcements (PA's) and requests for applications (RFA's) developed by the committee and sponsored by more than one Institute. Committee representatives are also encouraged to have their individual Institutes develop program announcements, requests for applications, and requests for proposals (RFP's). The majority of the RFA's and RFP's are developed by individual institutes.

In order to expand the support of nutrition research the NIH has published, through the NCC and individual Institutes mostly, 37 PA's, 45 RFA's, and 53 RFP's, for a total of 135 since June 1977. Joint PA's have been developed with the Alcohol, Drug Abuse and Mental Health Administration. These joint programs consolidate the needs of nutrition research and bring to the attention of the scientific community areas of research that need to be expanded. Investigator initiated projects are emphasized. Figure 6 shows the number of PA's, RFA's, and RFP's published by NIH from FY 1977 through FY 1984 in the area of nutrition research. As can be seen, there has been a dramatic increase over time, with 47 PA's, RFA's, and RFP's published in FY 1984 compared to three RFA's and RFP's in FY 1977.

#### **PAs, RFAs, AND RFPs IN NUTRITION RESEARCH AND TRAINING ISSUED BY NIH, FY 1977-1984**

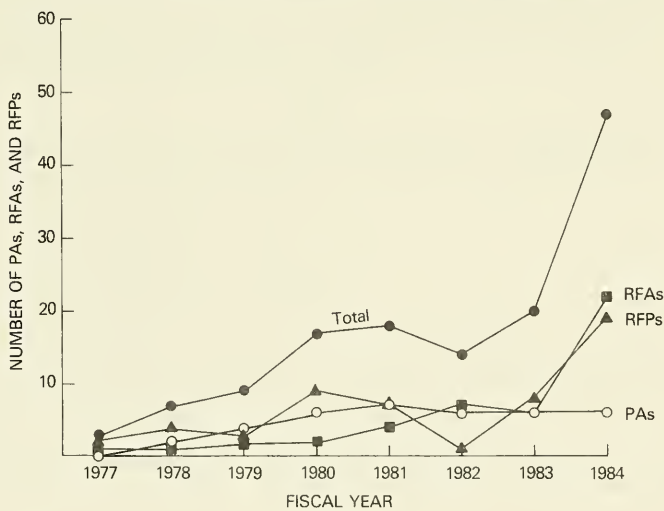


Figure 6

Table II presents selected PA's, RFA's, and RFP's published from FY 1977 through FY 1984, that best indicate the trends in nutrition research. As can be seen, major programs have been developed on the composition of human milk, nutritional requirements throughout the life cycle including aging, obesity, nutrition and cancer, lipids and cardiovascular disease, sodium and hypertension, nutrition and genetics, nutrition and renal disease, food allergy, nutrition and dental caries, and nutritional status assessment. As a result, the number of projects that are entirely (100 percent) nutrition research has been increasing. In FY 1984, 60 percent of expenditures of the NIH nutrition research program were for projects that were 100 percent nutrition, an additional 22 percent were determined to be between 50 and 99 percent nutrition, and only 18 percent were less than 50 percent nutrition.

The majority of the support for nutrition research is in the category of investigator initiated research. Center support in nutrition falls behind that for the NIH as a whole, 9 percent and 14 percent, respectively.

TABLE II

SELECTED PA's, RFA'S, RFP's IN NUTRITION RESEARCH AND TRAINING  
PUBLISHED IN THE NIH GUIDE FOR GRANTS AND CONTRACTS, FY 1977 - FY 1984

<u>1977</u>
In Vivo Quantification of Body Nitrogen
Quantification of Changes in Body Composition in Cancer Patients
Infant Nutrition
<u>1978</u>
Human Milk Bank Research and Distribution Center
The Role of Nutrition in the Rehabilitation of Cancer Patients
Validation and Standardization of In Vitro Techniques to Assess the Effect of Diet/Nutrition on the Mutagenic/Carcinogenic Potential of Human Secretions and Excretions
Interactions of Diet/Nutrition and the Use of Genetically Distinct Animals Strains in Carcinogenesis Studies
Development and Validation of Standard Procedures for the Nutritional Assessment and Monitoring of Adult and Pediatric Cancer Patients and Normal Individuals
Nutrition in Relation to Health of the Aged and Aging Process
Nutritional Aspects of Cancer and Its Etiology/Prevention, Treatment, Rehabilitation and Training
<u>1979</u>
The Effect of Diet on the Metabolism, Structure, Composition, and Blood Levels of High Density and Other Lipoproteins
Research Grant Support in Nutrition
Studies on Overnutrition and Obesity
Prevalence and Impact of Nutritional Individuality
Core Grants for Clinical Nutrition Research Units (CNRU's)
Metabolic Basis of Nutritional Individuality
Nutritional Individuality and Dietary Patterns

(Table II Continued)

National Research Service Awards for Individual Postdoctoral Fellowships in Nutrition

National Research Service Awards for Institutional Grants in Nutrition

1980

Nutritional Status and Non-Respiratory Lung Function

Diet, Nutrition, and Cancer Program Announcement of Research Interests in Alcohol and Cancer

Regional Training Workshops for Nutrition Counseling in Hyperlipidemia for Dietitians and Nutritionists

Evaluation of Regional Training Workshops for Nutrition Counseling in Hyperlipidemia for Dietitians and Nutritionists

Methodology for Estimation of Human Dietary Sodium Intake or Excretion

Developmental Aspects of Behavior and Nutrition

Research Study to Synthesize and Develop Noncariogenic Sweeteners that May be Used as Dietary Sucrose Substitutes

Studies to Identify, Isolate, Develop and Test Naturally Occurring, Noncariogenic Sweeteners that May be Used as Dietary Sucrose Substitutes

Clinical Trial of Fluoride in Osteoporosis

Workshop Announcement for Digestive Diseases and Nutrition

The Effects of Exposure to Westernization on Infant Feeding Patterns Among Nomadic Populations

1981

Human Milk Banking Studies

Fractionation, Identification and Characterization of Components of Colostrum and Human Milk

Clinical Studies on Human Milk

Relationship of Dietary Intake to Caries Incidence

NIH New Investigator Research Award (NIRA) in Nutrition. ADAMHA Special Notification for Research on Nutrition and Behavior

(Table II Continued)

Identification of Cariogenic Elements of Foods

Mechanisms in Food Allergy

Dietary Sodium and Its Role in the Prevention and Management of Hypertension

Diet and Nutrition Research [Dental Caries]

Health and Effective Functioning in the Middle and Later Years

1982

Research Grant Support in Nutrition: Environmental and Host Factors Affecting Nutritional Requirements

Long-term Effects on Infants of Hypochloremic Metabolic Alkalosis Resulting from Infant Formulas Deficient in Chloride (Amendment of Solicitation

Studies on Nutritional Support of the Patient

The Role of Natural Inhibitors in the Prevention of Cancer

Asthma and Allergic Disease Centers

Dietary Sodium and Its Role in the Prevention and Management of Hypertension

Clinical Trial of the Effect of Prenatal Fluoride Supplements in Preventing Dental Caries

Fluoride and the Prevention of Root Surface Caries

'Accuracy' of Questionnaire Derived Historic Dietary Information

1983

School Health Promotion for Cardiovascular Health of Children and Adolescents

A Prospective Study of the Frequency and Duration of Infant-Feeding Practices Among Primiparae

Effect of Severe Dental Fluorosis on the Oral Health of Adults

Successive Small-For-Gestational Age Births: A Longitudinal Study of Fetal Growth and Perinatal Outcome

Cooperative Agreements for Risk Reduction Clinical Trials  
Examining the Role of Micro and Macronutrients in the Prevention of Cancer

(Table II Continued)

Health and Effective Functioning in the Middle and Later Years  
(reissue)

Cooperative Agreements for a Phase III Trial of a Low Fat Diet  
in Women with Stage II Breast Cancer

Cooperative Agreement: Cooperative Clinical Study of Dietary  
Modification on the Course of Progressive Renal Failure

1984

Specialized Caries Research Centers

Sodium Sensitivity and Blood Pressure Response

A Phase III Trial of a Low Fat Diet in Women at Increased Risk  
for Breast Cancer

A Case Control Study of Vitamin Supplementation and Neural  
Tube Defects

Data Coordinating Center for a Case Control Study of Vitamin  
Supplementation and Neural Tube Defects

International Food Composition Data System

The Role of Micro and Macronutrients in the Prevention of Cancer

Methodology and Analysis of Fiber Components in Food

Data Coordinating Center for Cooperative Clinical Study of  
Dietary Modification on the Course of Progressive Renal Disease

NHLBI Nutrition Data System

Oral Contraceptives, Folate and Cervical Dysplasia

Studies in Obesity

Obesity and Cancer Risk in Women

Nutrition Intervention Trial in Linxian, China

Dietary Markers for Epidemiologic Studies of Cancer

Rat Pancreatic Exocrine Lesions: Biological Nature and Possible  
Role of Vegetable Oil in Formation of These Lesions in Gavage  
Studies

Metabolism and Physiology of Retinoids and Carotenoids in Humans



(Table II Continued)

Perinatal Emphasis Research Center-Intrauterine Growth Retardation
The Analysis of Relationships Between Growth and Dietary Intake Using NHANES Data
Core Grants for Clinical Nutrition Research Units
The Modification of Eating Behavior and Cancer Prevention
Methodology and Analysis of Vitamin A and Carotenoids in Foods
Mutagens in Human Foods
The Physiochemical Effects of Dietary Fiber in Humans
Isotretinoin Basal Cell Carcinoma Prevention Study

To vigorously expand research in clinical nutrition, the NCC developed the concept of a unique program based on Clinical Nutrition Research Units (CNRU's). In January 1979, an RFA entitled "Core Grants for Clinical Nutrition Research Units (CNRU's)," published jointly by NCI, NIADDK, and NIA, led to funding of four of these units in FY 1979 and three additional units in FY 1980. These seven CNRU's, which continued to receive support in FY 1984, are designed to provide a milieu for research, training, and education through coordinated effort, intellectual stimulation, and the sharing resources. A CNRU is an integrated array of research, educational, and service activities that is oriented toward human nutrition in health and disease. It serves as the focal point for clinical nutrition research activities and for the stimulation of high quality research in areas such as improved nutritional support of acutely and chronically ill persons, nutritional support of the hospitalized patient, assessment of nutritional status, effects of disease states on nutritional needs, and effects of changes in nutritional status on disease. Each CNRU must support the following seven components: research with human subjects and populations; laboratory investigations; research training; shared facilities and research services; education programs for medical students, house staff, practicing physicians, and paramedical personnel; nutritional support services; and public information activities.

The CNRU program, now in its fifth year, has been very successful in strengthening a multidisciplinary research program in clinical nutrition and in improving the educational program for medical students as well as other health professionals. In addition, the CNRU program has provided support for the training of new clinical investigators and the development of nutrition education materials for patients and the general public. The importance of the CNRU program has been recognized by the President's Science Advisor in the Office of Science and Technology Policy, Congress, and the General Accounting Office in

their reports. Most recently, the National Academy of Sciences-National Research Council's Food and Nutrition Board, Committee on Nutrition in Medical Education report on Nutrition Education in U.S. Medical Schools states: "The committee acknowledges the federal government's support for the training of faculty in nutrition and recommends that such funding be continued and increased. For example, the committee recommends that NIH consider increasing the funding for such programs as the Clinical Nutrition Research Units, which focus on training, research, and nutrition education activities."<sup>1</sup>

Because of the success of the CNRU program, the RFA was reissued to expand the program. NCI, NIADDK, and NIA again participated in the revised RFA entitled "Core Grants for Clinical Nutrition Research Units," which was published in the NIH Guide for Grants and Contracts in August 1984.

### Scientific Seminars

In order to keep its members abreast of important scientific developments, the NCC conducts a scientific seminars series that brings outstanding scientists from the intramural program of NIH, other agencies, and the scientific community together to present their research for thorough review and discussion. The topics and speakers are selected by the Committee, and the seminars comprise the second half of the monthly meeting of the NCC.

A series of these seminars has been dedicated to obesity, a major public health problem. The relation of body weight to health and longevity is a subject that has been of interest to the NCC for some time. In order to focus on obesity and review this subject in depth, this series has included the following eight presentations:

- o Animal Models for Human Nutrition Research, presented by Carl Hansen, Ph.D., Geneticist, Veterinary Resources Branch, Division of Research Services, NIH
- o Parental Factors in Childhood Weight Control, presented by Leonard Epstein, Ph.D., Associate Professor of Psychiatry, Epidemiology and Psychology, Western Psychiatric Institute and Clinic, University of Pittsburgh
- o The Psychology and Physiology of Obesity, presented by Kelly Brownell, Ph.D., Associate Professor of Psychiatry, University of Pennsylvania
- o Childhood Obesity, presented by William Dietz, M.D., Ph.D., Director of Clinical Nutrition, Division of Pediatric Gastroenterology and Nutrition, Tufts New England Medical Center

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<sup>1</sup> Nutrition Education in U.S. Medical Schools. Committee on Nutrition in Medical Education, Food and Nutrition Board, Commission on Life Sciences, National Research Council. National Academy Press, Washington, DC (1985).



- o Obesity as a Risk factor for Cardiovascular Disease, presented by Helen B. Hubert, Ph.D., Epidemiology and Biometry Program, NHLBI
- o The Effect of Exercise on Food Intake, presented by Xavier Pi-Sunyer, M.D., Associate Professor of Medicine, Columbia University, and Chief of Endocrinology, St. Luke's-Roosevelt Hospital
- o Dietary Fat, Carbohydrate Balance, and Weight Maintenance, presented by Jean-Pierre Flatt, Ph.D., Professor of Biochemistry, University of Massachusetts Medical Center
- o Dietary Fat and Neoplasia--The Role of Net Energy on Enhancement of Carcinogenesis, presented by Michael Pariza, Ph.D., Chairman, Department of Food Microbiology and Toxicology, Associate Director of Food Research Institute, University of Wisconsin

Because of the public health importance of obesity, the NCC developed a joint Program Announcement with ADAMHA titled "Studies on Obesity" in order to address the many research questions related to the etiology, prevention, and treatment of this multifaceted disease. Three Institutes of ADAMHA and six Institutes of NIH are participating in this very important PA which was published in March 1984. The NCC also sponsored two conferences in the area. The first, a workshop on "Body Weight, Health, and Longevity" was held in January 1982. The second, the "Satellite Conference on the Outpatient Management of Obesity" was held in October 1983, in conjunction with the Fourth International Congress on Obesity.

It has been an exciting and productive 8 years for the NCC. The interest and support of the Directors of NIH, combined with the cooperative spirit of the Institutes, has led to the expansion of the nutrition program. A great deal of work has been done by the Committee, which is rightfully proud of its accomplishments. The NCC looks forward to the future with enthusiasm and with continued determination to maintain the high standard of research established by the NIH.

A list of reports developed by the NCC Office follows, so that interested readers can acquaint themselves in detail with special reports including those developed by the Joint Subcommittee on Human Nutrition Research and the reports to the Congress on the Human Nutrition Research and Information Management System, as well as the annual reports of the NCC.

#### Reports Published by the Nutrition Coordinating Committee Office

##### Special Reports:

The Biomedical and Behavioral Basis of Clinical Nutrition--A Projection for the 1980s. NIH Publication No. 80-1970, November 1979.

NIH Report on FY '79 Spending Plans in Nutrition Research and Training. Published by NIH, March 1979.

The Politics of Nutrition, Seminar Report. NIH Publication No. 81-2278, January 1981.

Federally Supported Human Nutrition Research, Training, and Education: Update for the 1980s. I. Human Nutrition Research and Training. Prepared by the Joint Subcommittee on Human Nutrition Research, OSTP. Am. J. Clin. Nutr. 34 (Supplement): 978-1030, May 1981.

Federally Supported Human Nutrition Research, Training, and Education: Update for the 1980s. II. International Human Nutrition Research. Prepared by the Joint Subcommittee on Human Nutrition Research, OSTP. NTIS Doc. No. PB82-231739, June 1982.

Federally Supported Human Nutrition Research, Training, and Education: Update for the 1980s. III. Nutrition Education Research and Professional Personnel Needs for Nutrition Education of Professionals and the Public. Prepared by the Joint Subcommittee on Human Nutrition Research, OSTP. NTIS Doc. No. PB82-231747, June 1982.

Plan of the Human Nutrition Research and Information Management (HNRIM) System. Transmitted to the Congress July 23, 1982.

Federally Supported Human Nutrition Research and Training FY 1980 - FY 1982. Prepared by the Joint Subcommittee on Human Nutrition Research, OSTP. NTIS Doc. No. PB84-211242, June 9, 1983.

Federally Supported Human Nutrition Research Units: Selected Papers from the First Annual Conference, December 16-17, 1982. Prepared by the Joint Subcommittee on Human Nutrition Research, OSTP. NTIS Doc. No. PB85-135390, June 10, 1983.

"5-Year Priorities for Nutrition Research and Training, by Institute" published as Appendix F to the Report of the NIH Program in Biomedical and Behavioral Nutrition Research and Training, FY 1983.

Progress Report to the Congress on the Human Nutrition Research and Information Management System, July 29, 1983. Transmitted to the Congress, August 3, 1984.

Second Progress Report on The Human Nutrition Research and Information Management System, August 31, 1984. Transmitted to the Congress, December 4, 1984.

Third Progress Report on The Human Nutrition Research and Information Management System, July 1, 1985. Transmitted to the Congress, August 23, 1985.

**Annual Reports:**

**Report of the NIH Program in Biomedical and Behavioral Nutrition Research and Training, FY 1977. Published by NIH, June 30, 1978.**

**Report of the NIH Program in Biomedical and Behavioral Nutrition Research and Training, FY 1978. NIH Publication No. 80-2092, June 1979.**

**Report of the NIH Program in Biomedical and Behavioral Nutrition Research and Training, FY 1979 NIH Publication No. 81-2092, June 1980.**

**Report of the NIH Program in Biomedical and Behavioral Nutrition Research and Training, FY 1980 NIH Publication No. 82-2092, June 1981.**

**Report of the NIH Program in Biomedical and Behavioral Nutrition Research and Training, FY 1981 NIH Publication No. 83-2092, June 1982.**

**Report of the NIH Program in Biomedical and Behavioral Nutrition Research and Training, FY 1982 NIH Publication No. 83-2633, June 1983.**

**Report of the NIH Program in Biomedical and Behavioral Nutrition Research and Training, FY 1983 NIH Publication No. 84-2633, June 1984.**





**II.**

**HIGHLIGHTS OF THE  
NUTRITION RESEARCH  
PROGRAM AND PROGRAM  
DEVELOPMENT**



## NUTRITION RESEARCH HIGHLIGHTS

Over the past year, significant advances have been made in a number of areas of nutrition research. These areas include studies on infant nutrition and the composition of human milk, nutrition and behavior, inborn errors of metabolism, the role of nutrition in the development of immune function, food allergy, coronary heart disease, nutrition and hypertension/blood pressure control, the role of heavy metals and essential minerals in amyotrophic lateral sclerosis and Parkinson's dementia, nutrition and aging, osteoporosis, nutritional therapy for senile macular degeneration and cataracts, the role of nutritional status on oral diseases and dental caries, and methods used for nutritional status assessment. The advances being made in each of these research areas are described below.

### Infant Nutrition

Genetics and various environmental influences, such as nutrition, play a role in the proper growth and development of infants and children. In the area of infant nutrition, a number of major contributions have been made toward establishing much of the benchmark normative data on the nutritional needs and physical growth of the normal infant during the postnatal period. However, investigators continue to attempt to ascertain more precisely the nutrient requirements for maintaining acceptable rates of growth and development of the low birth weight premature and growth retarded infant. Studies are under way to examine food consumption, energy expenditure and growth, as well as nutrient interactions in the management of the low birth weight infant. Indirect techniques (such as stable isotopes) and a new electromagnetic device to measure fat free mass of infants also are being investigated for use as measures of infant growth and body composition.

Studies on the composition of human milk have provided invaluable data on the nutritional, antimicrobial, and growth-promoting factors or functional properties of components of human milk. For example, studies on the purification and characterization of growth factors in human milk have shown that human milk contains three species of growth factor, one of which plays a role in stimulating the development of the intestinal lining of the newborn. The HMFG III growth factor which has been purified to homogeneity has a molecular weight of about 6,000 and constitutes over 75 percent of the total growth factor activity in human milk. Purified HMFG III has been shown to stimulate DNA synthesis in 3T3 cells at a concentration of about 25 nanograms/-milliliter. Thus, this growth factor appears to stimulate growth of the cell type that lines the intestine. This proliferative process is critical to the intestine's protective mechanisms and to digestive function.

In addition, research in animals has shown that HMFG III significantly reduces the incidence, number, total length, and severity of cysteamine-induced duodenal ulcers. HMFG III appeared to yield an ulcer index similar to atropine. The discovery of this new biological activity in human milk points to exciting prospects for future



studies. Efforts will be directed toward establishing whether animals are protected from cysteamine-induced ulcers by HMFG III in their drinking water.

In order to better understand the significance of human milk in terms of its role in the growth and development of infants, the methods used to isolate and examine milk fractions must be considered. Variations in milk collection techniques, milk storage conditions, and analysis methodology have confounded efforts to compare the results of studies being reported by different laboratories. In addition, maternal factors that are often unreported contribute substantially to changes in milk composition that can further confound scientific evaluation.

The physical and mental development of infants with various kinds of malnutrition including protein calorie malnutrition, specific nutrient deficiencies and excesses, or malnutrition brought on by inborn errors of metabolism are also important research areas. A prospective multidisciplinary intervention study of children at risk of malnutrition has investigated the effects of malnutrition and environmental deprivation on child development in order to establish if it is possible to prevent retardation of physical and psychological growth by food supplementation and/or maternal tutoring. The study participants included the families and offspring of pregnant women from the southern barrios of Bogota, Columbia. The 456 families enrolled were randomly assigned to one of the following six groups varying in terms of supplementary feeding plans and normal stimulation or tutoring: 1) no treatment controls; 2) supplementary feeding of the infant from 6 months to 3 years of age; 3) supplementary feeding from 6 months of gestation to 6 months of age; 4) supplementary feeding from 6 months of gestation to 3 years of age; 5) a home intervention program designed to increase maternal psychological stimulation of the child but no supplementary feeding; and 6) supplementary feeding from 6 months of gestation to 3 years of age plus psychological stimulation. Results to date show significant effects of nutritional supplementation on birth weight, physical growth, maturation and locomotor development, while early stimulation affected cognitive performance. This major international study has contributed important information about nutritional deprivation, the effects of food supplementation, and the possible role of psychological stimulation of deprived children and their families. The study of the effect of malnutrition on children's mental development and its remediation is one of the most important issues in child health.

Other investigators, studying the effects of postnatal undernutrition on the cellular basis of hypomyelination in the developing rat brain, have recently found that in undernourished brain cells there appears to be an abnormal distribution of endoplasmic reticulum which is possibly a sign of oligodendroglia arrest. Such an arrest is likely to contribute to the hypomyelination found in the brains of undernourished infant rats. Another impressive finding has been that abnormally large axons may be a clue to the hypomyelination disorder, since in such large axons, compensatory increases in the myelin lamellae are absent.

Recent studies of infants with acute diarrhea have demonstrated that the volume and duration of diarrhea can be reduced dramatically by using oral rehydration solutions (ORS) containing hydrolyzed whey protein. It has been observed that hydrolyzed whey protein improves sodium resorption from the gut, reverses the secretory process, and thereby reduces diarrhea.

The rationale for using oral rehydration solutions to manage vomiting and diarrhea associated with acute gastroenteritis is based on the discovery made 20 years ago that intestinal sodium absorption is increased by a combination of actively transported sugar, such as glucose, with an actively transported amino acid, such as glycine. Early clinical studies in adult cholera patients demonstrated that the use of an oral rehydration solution containing both glucose and glycine markedly decreased the duration and volume of diarrhea when compared to the use of a solution containing only one of the substrates. Other studies also demonstrated the safety and efficacy of ORS's containing 90 nanomoles/liter of sodium and 20 grams/liter of glucose for hydrating hospitalized infants in both developing and developed countries.

In FY 1984, the results of a controlled clinical trial conducted in U.S. children indicated that a oral rehydration solution containing 50 or 30 nanomoles/liter of sodium can be used safely for the treatment of mild acute diarrhea, and that citrate is as efficacious as bicarbonate in the correction of acidosis. Until the results of this trial became available, many pediatricians were reluctant to use ORS containing "high" concentrations of sodium (90 nanomole/liter) for fear of inducing hyponatremia.

Studies on appropriate oral rehydration solutions for use in developing countries imply that such solutions be made from rice since it is a source of both carbohydrate and protein. This solution will not only replace the fluid and electrolyte loss, but will also decrease or stop the diarrhea entirely in children suffering from acute infectious gastroenteritis.

#### Nutrition and Behavior

In the area of nutrition and behavior, investigators are studying the neural mechanisms in animals that control the development of ingestion. Studies have shown that starting at 1 day of age, milk-deprived animals will actively eat when milk is infused into the front of their mouths. These animals do not utilize the usual response employed in getting milk during suckling, but instead lick and mouth like adults in order to move milk to the back of their mouths for swallowing. This finding of early independent ingestion indicates that this behavioral system is continuous with the adult ingestion motivation system, and is neurologically intact at birth.

#### Inborn Errors of Metabolism

Studies on the various inborn errors of metabolism are under way to investigate appropriate dietary manipulations that can be used in

order to bypass the enzymatic defects that characterize the inborn errors such as phenylketonuria, galactosemia, urea cycle enzyme deficiencies, and maple syrup urine disease. PKU, the inborn error in which individuals are unable to convert phenylalanine into tyrosine, affects 1 in every 14,000 births--or five newborns a week in the U.S. Since the early 1960's, neonatal screening programs have been successful in identifying most infants with PKU within a few weeks of birth. Initiation of a low phenylalanine diet soon after birth has prevented thousands of infants from developing the severe intellectual and neurological handicaps characteristic of untreated PKU.

Ironically, advances in early diagnosis and treatment of PKU have created new challenges. For example, over the past 20 years most young women with PKU who discontinued the low phenylalanine diet before they reached puberty have developed normally, both physically and intellectually. However, it appears that these young women, when consuming a regular diet during pregnancy are at a high risk of having a child with microcephaly (small head), mental retardation, and other devastating defects, even though the child does not have PKU. For example, a recent international survey showed that among approximately 138 offspring of women with no dietary management of their PKU during pregnancy and with blood phenylalanine concentrations of 20 milligrams/deciliter or higher, 92 percent of the offspring were mentally retarded, 73 percent had microcephaly, 12 percent had congenital heart disease, and 40 percent had a birth weight of 5½ pounds or less.

Results from animal studies also suggest that a phenylalanine level that is safe for the mother may be detrimental to the health of the developing fetus. Clinical investigations conducted to date on the effects of diet therapy provided to pregnant phenylketonuric mothers on the development of their offspring have provided conflicting results. In some cases, there appears to be no evidence of fetal effect, whereas in others, neonatal death due to congenital heart disease has resulted.

In order to determine the best method of managing women with controlled PKU during pregnancy, a 7-year study is under way in four clinical centers involving approximately 40 states across the U.S. This cooperative study, designed to reduce the high rate of mental retardation and congenital defects in the offspring of mothers with controlled phenylketonuria, seeks to determine: the level of maternal phenylalanine that will maintain a normal pregnancy; at what stage of pregnancy a low phenylalanine diet is most effective in preventing the effects of maternal PKU on the developing fetus; whether initiation of the diet before rather than after conception improves the baby's outcome; whether the diet reduces the frequency of mental retardation and other complications found among infants of PKU mothers; and the effect that the maternal blood levels of the amino acid tyrosine and such micronutrients as zinc have on pregnancy outcome. The results of this study will be particularly valuable in understanding the role of diet in the prevention of the neurological and behavioral problems associated with PKU.



Cholestasis in children (a failure of bile flow usually caused by congenital abnormalities of bile ducts in the liver) often results in symptoms related to deficiencies of the fat-soluble vitamins. A neurological disorder associated with a vitamin E deficiency before the age of 2 years has most recently been described. The clinical signs of the disorder, which include failure to control eye and skeletal muscles, are reversible only if vitamin E repletion is initiated soon after the signs appear. Thus, close surveillance of these patients for early signs of the deficiency is mandatory and must be coupled with aggressive efforts to prevent or reverse these deficiency signs.

### Nutrition and Immune Function

Proper nutrition as it affects the development of immune function is critical to the establishment of resistance to infection, particularly early in life. One investigator has shown that in animal models the zinc status of the fetus during the last two-thirds of pregnancy is carried over to the newborn period. In fact, experimentally induced zinc deficiency and resulting immune deficiencies persist for at least three generations.

### Food Allergy

The evaluation of reactions after food ingestion is one of the more challenging problems in allergy and immunology practice. The extensive differential diagnosis, absence of definitive diagnostic procedures, and lack of a satisfactory prophylactic therapy contribute to the difficulties. The clinical expression of food allergy or food hypersensitivity is the result of a series of interactions between ingested food antigens, the digestive tract, tissue mast cells, circulating basophils, and the food-specific antigen IgE. The clinical management of food allergy rests on the identification and removal of offending agents (foods) and the treatment of adverse reactions.

One study of this complex subject completed during FY 1984 involved 45 adult patients with a history of immediate adverse reactions following food ingestion. The patients were evaluated by history, physical examination, laboratory studies, and skin testing. The majority of their reactions involved the gastrointestinal tract alone or in combination with the skin or respiratory tract. The most frequently involved foods were shellfish, peanuts, eggs, fish, tomatoes, and walnuts. The results of the study suggest that an immediate adverse reaction to a food may have its initial presentation when the individual has reached adulthood, that such individuals tend to be atopic, that three or fewer foods are generally implicated, and that such sensitivities may persist for years. Thus, it seems likely that patients who have experienced previous food hypersensitivity reactions involving combined gastrointestinal, respiratory, and dermatologic symptoms, and who have a positive skin test to the suspected food, are more likely to experience another reaction upon subsequent exposure to that food.

In light of the evidence that a subset of severe asthmatics react adversely to sulfites with an increased difficulty in breathing, another study is under way to explore the possibility that individuals with recurrent idiopathic anaphylaxis and systemic mastocytosis are also sulfite sensitive. The patients suffering from these diseases are given increasing amounts of sulfites in capsule form. In approximately thirty cases examined to date, clinical reactions to sulfite have been negative. These preliminary data suggest that the majority of patients with idiopathic anaphylaxis and those with systemic mastocytosis are not sensitive to sulfites.

### Coronary Heart Disease

Coronary heart disease (CHD) remains the major cause of death and disability in the U.S. and in other industrialized countries. Epidemiological studies have established that the higher the plasma total or low density lipoprotein cholesterol level, the greater the risk that coronary heart disease will develop. The Lipid Research Clinics' Coronary Primary Prevention Trial (LRC-CPPT) was undertaken to answer the important question of whether the lowering of plasma cholesterol in hypercholesterolemic men would reduce their risk of developing CHD. 3,806 asymptomatic middle-age men with primary hypercholesterolemia were randomly assigned to the bile acid sequestrant cholestyramine or to placebo. Treatment assignment was double blind and both groups followed the same moderate cholesterol-lowering diet. The average followup of participants was 7.4 years, and the average cholesterol levels in the cholestyramine group were reduced 13.4 percent, 8.5 percent greater than in the placebo group. These levels were associated with a statistically significant 19 percent reduction in definite CHD death and/or definite nonfatal myocardial infarction. The degree of reduction of coronary risk was related to the amount of cholesterol lowering. Coronary heart disease incidence in men who sustained a 25 percent fall in cholesterol was half that of men who remained at pretreatment levels.

In general, CHD incidence fell 2 percent for every 1 percent fall in cholesterol and the incidence rates for new positive exercise electrocardiograms, angina, and coronary bypass surgery were also reduced. These findings were presented at a press briefing on January 12, 1984, and were published in the January 20th issue of the Journal of the American Medical Association.

A number of investigators continue to examine the effects of specific dietary components on the incidence of cardiovascular disease. One exciting area of growing scientific interest is the study of the effects of diets high in fish oil which contain long chain polyunsaturated fatty acids of the omega-3 series on cardiovascular disease, particularly atherosclerosis both in specific populations such as the Eskimos and in hypertensive and diabetic nonhuman primates. Studies have suggested that the atherosclerosis-sparing effect of dietary fish oil could be attributed to one of its fatty acids, eicosapentanoic acid, and its preferential incorporation into the platelet-membrane phospholipids. This incorporation appears to change platelet function in ways favorable to diminishing thrombosis. Other studies are

investigating this phenomenon in terms of the effects of a fish oil diet on the natural history of arteriosclerosis in monkeys. Such findings have also been observed in studies of Eskimos who consume large quantities of fish oils. The fatty acids are considered to have special effects upon plasma lipid and lipoprotein levels, particularly triglycerides and VLDL, and platelet function. In spite of large quantities of cholesterol contained in the Eskimo diet, the incidence of atherosclerotic disease in these people is low, and death due to cardiovascular diseases such as myocardial infarction, aortic aneurysms, and cerebrovascular accidents constitutes only 1-2 percent of the total death rate.

#### Nutrition and Hypertension/Blood Pressure Control

The relationships between nutrition and hypertension, and blood pressure control have been important areas of research interest for many years. In order to identify the research issues, questions and objectives that could strengthen the scientific understanding of these relationships, the annual nutrition conference sponsored by the NCC in FY 1984 focused on the various aspects of "Nutrition and Hypertension." The importance of research in this area as defined by the organizing committee and the workshop participants, and the conclusions resulting from the workshop are described on pages 80-81 of this report.

#### Trace Elements

During the past decade, a number of studies have systematically investigated the potential causal role of heavy metals and essential minerals in the high incidence of amyotrophic lateral sclerosis (ALS) and parkinsonism-dementia (PD) among the Chamorro people of Guam. Long-term epidemiologic and genetic studies suggested a place-disease phenomenon and led to the discovery of unusually low concentrations of calcium and magnesium in garden soil and drinking water, not only in Guam, but also in the southern coastal plain of West New Guinea and in the Kii Peninsula of Honshu Island in Japan, where a high incidence of ALS and parkinsonism exists. These results complement the recent findings of disturbances in calcium and vitamin D metabolism in Guamanian patients with ALS and PD, of cortical bone loss in Guamanian children and adults, and of intraneuronal accumulation of calcium and aluminum in brain tissues from affected patients.

The evidence to date supports the hypothesis that defects in mineral metabolism and secondary hyperparathyroidism, provoked by chronic nutritional deficiencies of calcium and magnesium, lead to increased intestinal absorption of toxic metals and deposition of calcium and aluminum in neurons. These studies and the recent confirmation of rapidly declining incidence rates for both ALS and PD, coupled with the lack of evidence for a primary genetic defect and the inability to transmit ALS and PD to nonhuman primates, strongly suggest the involvement of toxic elements and essential minerals in the disease process.



The nutritional and metabolic significance of selenium is also under investigation. Selenium is an essential nutrient which if deficient is known to be an etiological factor in a cardiomyopathy that occurs in Chinese children. Selenium status may also have an effect on other diseases, including cancer. Although an essential constituent of glutathione peroxidase, selenium has a number of biological effects that cannot be explained by this enzyme. These include its effect on a number of xenobiotic-metabolizing enzymes, heme metabolism, diquat-induced lipid peroxidation, and glutathione synthesis and release by the liver. For example, selenium deficient rats synthesize and release into the plasma twice as much glutathione as controls. A number of products of glutathione breakdown are being tested for their activity in diminishing glutathione release by a selenium-deficient liver. It is known that glutathione is removed from the plasma by the kidney and that its extraction by the selenium-deficient kidney is less efficient than by normal kidneys. Perfused kidneys from selenium-deficient and control rats are being studied to learn whether selenium deficiency affects glutathione release and extraction.

### Nutrition and Aging

Nutrition is certainly one of the important environmental factors that exert chronic influence on the aging organism. Laboratory and clinical studies are under way to examine the effects of aging on nutrient requirements, absorption and metabolism, as well as the effect of diet on the natural history of diseases common in the elderly such as osteoporosis, diabetes, blindness, cancer, hypertension and atherosclerosis.

One study of healthy free-living elderly men and women revealed that iron deficiency and anemia were not any more prevalent in this age group than in young adult populations. The anemia which is seen often in studies of the elderly appears to be explained more by health status, diet, race and socioeconomic status than age per se.

Another study using rats as a model to delineate metabolic changes with age found that vitamin D<sub>3</sub> absorption was not reduced by age. If this is true for humans, then vitamin D malabsorption would not appear to be a likely cause for the metabolic bone disease that is commonly seen with aging. Other studies continue to explore the role of fluoride in normal skeletal and dental growth. Excessive amounts of fluoride usually cause abnormal increases in skeletal mass. Recent studies have shown that fluoride acts directly on bone cells; e.g., chick bone cells treated with sodium fluoride increased both in number and in activity of alkaline phosphatase, an enzyme that reflects activity of bone cells. These studies also showed an increased growth of embryonic chick bone in organ culture. As a result of these studies and other clinical investigations, it seems that fluoride may be helpful in the treatment of most patients with osteoporosis.

Osteoporosis is a major public health problem and affects as many as 15-20 million individuals in the United States, attributing to 1.3 million fractures annually in people aged 45 years and older. The cost of osteoporosis in the U.S. has been estimated at \$3.8 billion



annually. Osteoporosis affects all bones, typically the spine, wrist, and hip, and appears to be due to those mechanisms underlying an accentuation of the normal loss of bone, which follows menopause in women, and occurs in all individuals with advancing age. Prevention of bone fractures in susceptible patients is the primary goal of intervention. Strategies prescribed to date include estrogen replacement in postmenopausal women, adequate nutrition, including an elemental calcium intake of 1,000-1,500 milligrams/day, and a program of modest weight-bearing exercise.

Research on osteoporosis is needed to examine the currently unanswered questions on the development and maintenance of bone as a tissue, i.e., those factors that control bone cell activity, and the regulation of bone mineral and matrix formation and remodeling. Clinical and epidemiological research studies are also needed to examine methods for practical prevention and treatment of the disease. The results of such research will provide a clearer understanding of appropriate therapies for this disease, even as current treatments are evaluated clinically.

Another age related disease, senile macular degeneration or age related maculopathy is being investigated in terms of whether nutritional therapy with vitamins E and C, along with special protective eyeglasses, can slow or halt its progression. This very common retinal disease can cause diminution or total loss of central vision. Laser treatment can benefit patients who are in the greatest danger of losing sight from this disease, however, preventive measures are needed that would keep people free of the disorder, or at least arrest it before it reaches a sight-threatening stage. If this new treatment approach proves to be of value, the incidence of visual handicaps among older people may be greatly reduced.

Age related cataracts is another problem of the elderly which may benefit from the protective effects of antioxidants such as vitamins E and C, and selenium. In addition to determining how these nutrients might protect the lens' proteins from the damaging effects caused by oxidants, a collaborative epidemiological study in India is investigating other various risk factors for the development of these cataracts. This study, based at the Rajendra Prasad Center for Ophthalmic Sciences of the All India Institute for Medical Sciences in New Delhi, includes a biochemical profile on patients drawn from a population in which the incidence of cataracts is far higher than in the United States. The profile includes the monitoring of blood levels of the aforementioned antioxidants as well as amino acids, other vitamins, and trace minerals. Results from this study are expected to help clarify the role of nutrition in cataractogenesis, and the possibilities for prevention or delay of onset through nutritional interventions.

Other studies are investigating the role of zinc and retinol binding proteins in the visual process. It appears that under normal conditions human and animal ocular tissue contain high concentrations of zinc. This essential mineral functions in a variety of ways and is an integral part of numerous metalloenzymes, including some that affect

vision. Studies in animal models are under way to investigate zinc metabolism in the retinal pigment epithelium (RPE) and photoreceptor outer segments (OS). Elucidating the effects of varied levels of dietary zinc on RPE and OS metabolism may lead to new insights on the possible role of zinc in human retinal dystrophies and therefore the nutrient requirements of the eye.

Retinol-binding proteins, both in the plasma and cells, are thought to regulate the transport and therefore the metabolism of vitamin A. These proteins and their response to dietary manipulations are being studied in eye tissue compartments in order to gain a better understanding of the biochemistry of the visual process and its alteration by diet and disease factors.

### Oral Disease/Dental Caries

The effect of oral diseases and stages of life, such as aging, are important factors affecting the nutritional status of individuals. Oral mucosal diseases such as herpes infections and aphthous ulceration; poor fitting dentures; loose teeth and oral surgical procedures can interfere with eating and compromise the general health and nutritional status of a patient at any stage of life. Salivary gland disease can affect the nutritional status of a patient by altering salivary composition and flow. Such changes, in turn, may affect taste and digestion, and influence food preference. The increasing use of dentures with age also affects mastication and the taste of foods, and may alter food choice and intake patterns in ways that result in clinical or subclinical states of nutritional deficiency.

It has been well documented that knowledge of an adequate diet alone is not enough to alter behavior. Since most oral diseases, except for oral cancer, are not seen as life threatening, dietary changes are more difficult to effect. Dietary intervention studies to determine the effectiveness of various techniques for the promotion of sound oral health are a growing area of research.

Epidemiological and experimental studies support the hypothesis that infectious diseases and nutritional deficiencies during tooth development increase an individual's susceptibility to dental caries. Pre-eruptive protein calorie malnutrition and vitamin A deficiency have each been shown to increase caries development in rats. And, the posteruptive provision of foods high in refined sugar can enhance the establishment, colonization, and metabolic activity of cariogenic microorganisms in dental plaque, despite the beneficial effects that may have been contributed pre-eruptively by a nutritious diet. Proteins can also affect plaque by providing basic amino acids that can neutralize the products of bacterial metabolism of sugars and also stimulate the rate of salivary flow. In turn, saliva can buffer acids produced by plaque bacteria or reduce the residence time of foods in the mouth and thus limit the availability of fermentable substrate to the plaque. More epidemiological studies are needed to evaluate the relationship between human nutritional status and periodontal diseases. Overall, nutrient deficiencies affect the severity and extent of periodontal diseases by modulating the response and repair properties

of the tissues. Inadequate nutrient intake could also affect the metabolism of plaque flora in the gingival crevice as well as systemic immunological responses to microbial antigens.

Salivary glands are an integral part of the digestive system because they secrete hydrolytic digestive enzymes which convert starch and other macromolecules into smaller molecules. Basic research is under way to investigate the functional development and regulation of salivary glands, the composition of saliva, and salivary gland secretions under normal conditions. Through these studies, insight will be gained into the basic mechanisms of salivary secretion related to digestion and nutrition.

Xerostomia, or dry mouth, is an area of particular interest because the decrease in salivary flow or alteration in the composition of saliva can have a profound effect on oral and dental health as well as on nutritional status. Sufficient saliva is needed for the formation of a chewed mass of food and to initiate the swallowing reflex. An ultrasound imaging machine is being used to diagnose swallowing disorders, and therefore to accurately find the cause of the problem so that effective therapies can be developed.

Another study is examining oral-pharyngeal tissues of bulimic patients in order to determine the incidence and severity of oral disease and salivary dysfunction. Bulimia, an eating disorder characterized by recurrent episodes of binge eating followed by self-induced vomiting, mainly affects young female adults of college age. Medical complications of this disorder include gastritis, esophagitis, severe dehydration, liver function abnormality, and various nutritional deficiencies.

Scientists studying the two digestive enzymes--lingual lipase and amylase--which are important in the digestion of fats and carbohydrates, have recently discovered them to be secreted from a gland in the tongue and have purified them using an animal model. Important information can now be obtained on the molecular properties of the enzymes, the secretory process in the gland, and the function of the gland in the oral cavity.

Interest in dietary approaches to oral diseases has already inspired some collaborative programs involving government agencies, professional groups, industry and academia. These studies have looked at the cariogenic potential of foods and sought ways to reduce cariogenicity. The development of noncariogenic sweeteners such as aspartame and saccharin, as well as the identification of anticariogenic components in food, such as factors in certain aged cheeses or extracts from certain seeds, are significant contributions of this research. Such findings set the stage for further production and promotion of food products that enhance oral health.

#### Methods for Nutritional Status Assessment

Research on nutritional status assessment includes investigations to develop and evaluate various methods useful to determine the require-



ments of essential nutrients throughout the life cycle and to determine easy ways to assess nutritional status in both normal and patient populations. One area where significant advances have been made is in the assessment of nutritional status of patients suffering from iron depletion anemia or from iron overload disorders (such as Cooley's anemia or hereditary hemochromatosis). These patients have abnormal levels of body iron that must be regulated. A magnetic device known as a superconducting quantum-interference device (SQUID) susceptometer, has been developed recently and can be used outside of the body to determine its iron content. The instrument allows for an earlier identification of patients at risk of iron overload. Until now, methods to assess the amount of body iron have depended on indirect, relatively insensitive techniques or invasive procedures such as liver biopsy. The new technique is direct, noninvasive, and more reliable, accurate, and practical than previous methods. Since the liver is one of the main sites of body iron storage and thus reflects the extent of iron accumulation by the body, the SQUID is placed on the abdomen directly over the liver and measures its iron content in less than a minute.

To date, approximately 200 patients have been tested with the instrument and many more are expected to be referred for the test by physicians in the U.S. and abroad. Candidates include patients with Cooley's anemia, aplastic anemia, porphyria, and liver and kidney diseases among other disorders.

Attempts to compare the results of various studies on the relationship of dietary habits and nutritional status and the incidence of cancer often have been inconclusive. One major impediment to the analysis has been the fact that the data from such studies is not comparable. In order to permit more accurate comparisons of environmental data among different studies, intramural investigators have developed a core questionnaire covering "Health Habits and History" for use in all studies, and supplemented by more specific questionnaires.

The core questionnaire includes questions under the categories of personal information; habits, usual eating and food habits; medical information; occupational information; family history; and other health factors which include physical and social activity. In June 1984, this questionnaire was reviewed by a group of experts who made a number of suggestions for revisions. The questionnaire is now ready for testing and validation. In addition to the core questionnaire, a core dietary questionnaire has been developed which is a major step toward ensuring comparability of dietary intake data in a variety of clinical and epidemiological studies.

Another important project related to making food composition data and dietary intake data more complete, accurate, and accessible has involved the development of the International Network of Food Data Systems (INFOODS). This project has proceeded from an outline of a plan to an international network of individuals actively working toward these goals. Specifically, a detailed plan of action has been drawn up and approved by an international group of scientists repre-

senting the World Health Organization, the Food and Agriculture Organization, United Nations University, and the International Union of Nutrition Sciences, among others. Regional INFOODS committees have been set up in Europe, North America and Asia, and additional preliminary meetings have been held to discuss the organization of a Latin American INFOODS group. These groups will contribute to and implement the activities of INFOODS, as well as develop relevant regional activities with the assistance of INFOODS.

International committees have been set up to work in the areas of terminology and data quality and international meetings have been scheduled for next year on the topics of terminology, data quality, users and needs, and information systems. Efforts to update and extend the FAO bibliography of food composition data has already begun. While major funding for this project is coming from NCI, NHLBI provides additional support, and the United Nations University has agreed to provide administrative support. A secretariat has been established at the Massachusetts Institute of Technology to coordinate all of the aforementioned activities related to INFOODS.

#### NHLBI's School-Based Research Initiatives For Health Promotion and Disease Prevention

During the past decade, NCI, NHLBI, NICHD, and NIDR have funded initiatives in school-based research for health promotion and disease prevention strategies related to cancer, cardiovascular disease, child health, dental caries and periodontal diseases. Many of these initiatives include a nutrition research component. For example, NCI supports research on nutrition and other lifestyle factors related to cancer prevention with many studies dealing with the physiological and psychosocial aspects of students with childhood cancers returning to school. NICHD supports research in preschool health promotion including safety and nutrition, and NIDR supports several studies among school-aged children that include research on the effectiveness of a school-based fluoride tablet or mouth rinse regimen in the prevention of dental caries and periodontal disease.

In FY 1984, NHLBI supported 15 school-based cardiovascular risk reduction studies which are highlighted in this section of the report. These studies fall primarily into the category of demonstration and education research of NHLBI which is designed to test the effectiveness of interventions to promote health or prevent cardiovascular disease in a defined population. The studies focus on interventions for one or more cardiovascular disease risk factors and primarily include nutrition, exercise, and smoking components. Of the 12 studies that have nutrition components, 10 also address exercise. The racial/ethnic groups in the studies involve black, white, and Hispanic populations, a Native American population, and two small Asian populations.

A social learning model is the predominant theoretical approach used in the studies. This model suggests that changes in specific environmental, personality and behavioral attributes are likely to influence changes in children's health behavior. In most studies, the schools

are randomized to treatment and control conditions with the same measures being tested both before and after intervention. The principal investigators for the studies are biomedical and behavioral scientist while the research teams are multidisciplinary. Outcomes are predominantly changes in knowledge, attitudes, behavior, and physiological measures. Several studies are focusing on school policy and procedure changes.

For the most part, classroom teachers who have received training are delivering the intervention programs, while in some cases additional trained resource people are being used. Peer teaching models are being tested in several studies. A variety of teaching methods and materials are being used with the majority incorporating skills' training and booster sessions. For example, the nutrition curricula being used in the Louisiana State University study is based on needs assessments, surveys and input from focus groups. The University of Texas study focuses on methods for assessing diet and exercise behaviors of students in grades three through five. In this study, data are also being collected on blood pressure, diet, urinary electrolytes, aerobic activity, pulse rate, and body composition. Analysis of the data will consider dietary correlates of differences in blood pressure across ethnic groups. In addition, the skill aspect of self-reporting diet and exercise behaviors is being examined. Both of these studies are investigating policy and environmental changes in the school vis-a-vis the school food service program serving as a focus for these institutional changes.

A majority of the studies also have a parent or family component as part of the intervention. For example, in the study under way at the University of California at San Diego, the family is recruited and the intervention is delivered to the family. The Baylor College of Medicine study has an extensive parent component and identifies family members at risk for heart disease and stroke. The University of Minnesota study will compare a cardiovascular disease nutrition curricula taught with and without parent involvement. The studies at Louisiana State University and the University of Pennsylvania involve parents in numerous components of their intervention program.

The study at the University of New Mexico is designed for a multicultural rural New Mexico population of fifth graders and concentrates on weight control and obesity, exercise, and smoking prevention. This is a curriculum project intended to combine elements from a number of curricula, selecting the best components of each and adapting these for the Native American population. The pilot data indicate that existing curricula require substantial revisions and development of new materials to meet the needs of this group of students and their families.

To date, the New York "Know Your Body" Program and the Chicago Heart Health Curriculum Program are the only two intervention studies that have reported major research results. The New York "Know Your Body" Program consists of a curriculum focusing on nutrition, physical fitness, and cigarette smoking prevention. The program was evaluated in 11 intervention and 11 control elementary schools. After 3 years



of intervention, the data from this research indicate that diastolic blood pressure and the total cholesterol to HDL ratio decreased more in the intervention than in the control students. The effectiveness of the "Know Your Body" Program is currently being tested in a Washington, D.C. study of predominately black urban children in grades four through six. Changes in the risk factors being tested include obesity, lack of physical exercise, a diet high in fats and salt, and cigarette smoking. Measurements being assessed include systolic and diastolic blood pressure, plasma total and high density lipoprotein cholesterol, ponderosity index, triceps skinfold thickness, post-exercise pulse recovery rate, as well as measures of knowledge, attitudes, behavior, and psychosocial moderators.

The purposes of the Chicago Heart Health Curriculum Program were to increase health knowledge related to risk factors for cardiovascular disease, to develop positive attitudes toward healthful living and self, and to encourage healthy behavior in sixth grade public school students in Chicago. In the Chicago "Body Power" Program, sixth grade students were taught learning modules in nutrition, exercise, smoking prevention, and general health knowledge. The study has shown that a cardiovascular risk reduction program designed for a multiracial urban population can be successfully implemented in a public school system, and parents and other family members will actively participate in such a school-based program along with teachers and students. Preliminary results indicate substantial knowledge gains, some positive attitude changes, but little or no measurable behavior change. Thus far, the study has provided important information on teaching methodology, knowledge gains, and short-term changes in attitudes and behavioral intentions of the students.

The results of this group of research studies will provide important insight on the role of school-based research initiatives in health promotion and disease prevention programs related to cardiovascular disease.

#### NEW PROGRAM ANNOUNCEMENTS, REQUESTS FOR APPLICATIONS AND REQUESTS FOR PROPOSALS IN NUTRITION

A major responsibility of the NCC is to identify areas for further research and bring them to the attention of the scientific community through the development and publication of program announcements (PA's), requests for applications (RFA's), and requests for proposals (RFP's).

In FY 1984, the number of nutrition announcements published by the Institutes tripled over last year and was significantly greater than in previous years. Forty-seven announcements were published in FY 1984 whereas 19 were published in FY 1983.

A PA is a formal statement of an NIH extramural research activity or of the initiation of a new or modified mechanism of support. It may describe new or modified program interests, or simply be a reminder of continuing interest.



An RFA is a formal statement which (a) invites grant applications in a well-defined scientific area to accomplish specific program purposes, (b) generally identifies only one application receipt date, and (c) indicates whether or not funds have been set aside for the competition and, if so, the amount of funds and/or the expected number of awards to be made. An RFA may be reissued as necessary.

An RFP is the government's invitation to prospective offerors to submit a contract proposal based on the terms and conditions set forth in the RFP by the statement of work that describes the nature of intended procurement. The number of contracts awarded as a result of an RFP is smaller than the number of applications funded as a result of PA's and RFA's.

Table III lists the 47 PA's, RFA's, and RFP's in nutrition published in FY 1984, with the origin and date of each announcement, the type of announcement, and its title. A brief description of each announcement is included in appendix H. Included in the table are 6 PA's, 22 RFA's, and 19 RFP's.

TABLE III

PA's, RFA's, and RFP's in Nutrition Research and Training  
Published In The NIH Guide For Grants and Contracts, FY 1984

<u>ISSUED BY</u>	<u>DATE</u>	<u>TYPE</u>	<u>TITLE</u>
NIDR	10/14/83	RFA	Specialized Caries Research Centers
NHLBI	10/14/83	RFA	Cardiovascular Disease Prevention in the Workplace
NHLBI	10/14/83	RFA	Sodium Sensitivity and Blood Pressure Response
NHLBI	10/14/83	RFP	Support of Analysis of LRC Program Clinical and Epidemiological Data Sets
NHLBI	10/17/83	RFA	National Research and Demonstration Centers and Specialized Centers of Research in Hypertension
NCI	11/3/83	RFP	Efficacy Studies of Chemopreventive Agents in Animal Models Including Synthesis, Bioavailability, and Encapsulation Studies
NHLBI	11/11/83	PA	Biobehavioral Sequelae of Antihypertensive Therapies
NIA	11/11/83	PA	Special Emphasis Research Career Award for Social and Behavioral Scientists in Geriatrics Research
NCI	11/11/83	RFA	A Phase III Trial of a Low Fat Diet in Women at Increased Risk for Breast Cancer
NCI	11/20/83	RFP	Phase I Studies of New Chemopreventive Agents
NICHHD	11/21/83	RFP	A Case Control Study of Vitamin Supplementation and Neural Tube Defects
NICHHD	11/21/83	RFP	Data Coordinating Center for a Case Control Study of Vitamin Supplementation and Neural Tube Defects
NCI	11/30/83	RFP	International Food Composition Data System
NCI	12/9/83	RFA	Biochemical Epidemiology

(Table III Continued)

ISSUED BY	DATE	TYPE	TITLE
NCI	12/9/83 (Revised)	RFA	The Role of Micro and Macronutrients in the Prevention of Cancer
NCI	1/4/84	RFP	Methodology and Analysis of Fiber Components in Food
NIADDK	1/6/84	RFA	Data Coordinating Center for Cooperative Clinical Study of Dietary Modification on the Course of Progressive Renal Disease
NHLBI	1/23/84	RFP	NHLBI Nutrition Data System
NICHD	2/3/84	RFA	Perinatal Emphasis Research Center - Perinatal Pharmacology and Toxicology
NIDR	2/3/84	RFA	National Research Service Awards for Institutional, Postdoctoral Training Programs in Caries Research
NCI	2/3/84	PA	The NCI Clinical Investigator Award
NCI	2/24/84	RFP	Investigations of Cervical Cancer in Latin America
NICHD	3/12/84	RFP	Prospective Physiological and Psychologi- cal Follow-Up of Offspring of Diabetic Mothers
NICHD	3/27/84	RFP	Oral Contraceptives, Folate and Cervical Dysplasia
NEI	3/30/84	PA	Basic Mechanisms in Retinal Phototoxicity
NIADDK, NCI, NHLBI NIA, NICHD NINCDS, NIAAA NIDA, NIMH	3/30/84	PA	Studies on Obesity
NCI	4/27/84	RFA	Obesity and Cancer Risk in Women
NCI	5/2/84	RFP	Nutrition Intervention Trial in Linxian, China
NCI	5/25/84	RFA	Dietary Markers for Epidemiologic Studies of Cancer
NIEHS	5/25/84	RFA	Rat Pancreatic Exocrine Lesions: Biological Nature and Possible Role of Vegetable Oil in Formation of These Lesions in Gavage Studies

(Table III Continued)

ISSUED BY	DATE	TYPE	TITLE
NCI	6/7/84	RFP	Evaluation of Chemopreventive Agents by In Vivo Screening Assays
NCI	6/29/84	RFA	Metabolism and Physiology of Retinoids and Carotenoids in Humans
NIA, NIAID NIADDK, NCI NICHD, NIEHS, NHLBI	6/29/84	PA	Clinical Investigator Award
NICHD	6/29/84	RFA	Perinatal Emphasis Research Center- Intrauterine Growth Retardation
NICHD	7/16/84	RFP	The Analysis of Relationships Between Growth and Dietary Intake Using NHANES Data
NCI, NIADDK, NIA	8/3/84	RFA	Core Grants for Clinical Nutrition Research Units
NCI	8/3/84	RFA	The Modification of Eating Behavior and Cancer Prevention
NCI	8/28/84	RFP	Methodology and Analysis of Vitamin A and Carotenoids in Foods
NCI	9/7/84	RFA	Mutagens in Human Foods
NCI	9/7/84	RFA	The Physiochemical Effects of Dietary Fiber in Humans
NCI	9/7/84	RFA	Innovative Approaches to Development of Cancer Chemopreventive Agents
NCI	9/7/84	RFA	Selected Cancer Prevention Clinical Trials
NHLBI	9/7/84	RFA	National Research and Demonstration Centers on Ischemic Heart Disease
NCI	9/7/84	RFP	Isotretinoin Basal Cell Carcinoma Prevention Study
NCI	9/10/84	RFP	Evaluation of Chemopreventive Agents by In Vitro Techniques
NHLBI	9/20/84	RFP	Community and Cohort Surveillance Program (CCSP) - Field Center
NHLBI	9/20/84	RFP	Community and Cohort Surveillance Program (CCSP) - Coordinating Center

## THE CLINICAL NUTRITION RESEARCH UNITS

The establishment of the Clinical Nutrition Research Unit has been one of the most important accomplishments of the NCC. The CNRU's form the basis of a new National Program in Clinical Nutrition Research. The RFA entitled "Core Grants for Clinical Nutrition Research Units (CNRU's)," published jointly by NCI, NIADDK, and NIA in January 1979, led to funding of four units in FY 1979 and three additional units in FY 1980. These seven CNRU's, which continued to receive support in FY 1984, are designed to provide the milieu for research, training, and education through coordinated effort, intellectual stimulation, and the use of shared resources.

Because of the success of the CNRU program, the RFA was reissued to expand the program. NCI, NIADDK and NIA again participated in the revised RFA entitled "Core Grants for Clinical Nutrition Research Units," which was published in the NIH Guide for Grants and Contracts in August 1984.

The CNRU program, now in its fifth year, has been very successful in strengthening a multidisciplinary research program in clinical nutrition and in improving the educational program for medical students as well as other health professionals. In addition, the CNRU program has provided support for the training of new clinical investigators and the development of nutrition education materials for patients and the general public.

A CNRU is an integrated array of research, educational, and service activities that is oriented toward human nutrition in health and disease. It serves as the focal point for clinical nutrition research activities and for the stimulation of high quality research in areas such as improved nutritional support of acutely and chronically ill persons, nutritional support of the hospitalized patient, assessment of nutritional status, effects of disease states on nutritional needs, and effects of changes in nutritional status on disease. Each CNRU must consist of the following seven components: research with human subjects and populations; laboratory investigations; research training; shared facilities and research services; education programs for medical students, house staff, practicing physicians, and paramedical personnel; nutritional support services; and public information activities.

In order to foster integration and support interactions among the seven CNRU's, NIH sponsors an annual meeting of the CNRU directors to discuss research progress and future research needs. The fourth annual meeting was held on January 9-10, 1984, hosted by the two CNRU's located in New York: the CNRU at Columbia University College of Physicians and Surgeons' Institute of Human Nutrition and the CNRU at Memorial Sloan-Kettering Cancer Center/New York Hospital-Cornell University Medical Center/Rockefeller University. Highlights of the meeting included in-depth presentations of the clinical nutrition research programs of the two host CNRU's, as well as tours of the research facilities.



The presentations featured discussions on biophysics, metabolism and metals, immunology, mass spectroscopy, and lipid laboratories. New clinical investigators presented highlights of their research which included topics such as calcium and bone metabolism in home total parenteral nutrition patients, and the effect of beta-adrenergic stimulation on thyroid hormone metabolism and energy expenditure in obesity. Research results from a number of pilot studies were also presented which included areas such as the nutritional requirements of the premature infant and infants in intensive care units, nutrition and drug metabolism in man, treatment of anorexia in cancer patients by enzyme-mediated depletion of serotonin, and magnesium metabolism and the renin-angiotensin-aldosterone system. Activities of the Nutrition Information Center and the Nutrition Support Service of the N.Y. Hospital/Cornell University Medical Center CNRU were also presented.

In order to provide participants at the meeting with an overview of ongoing clinical nutrition research programs under way at all seven CNRU's, the directors of the CNRU's at the Medical College of Georgia, the Universities of Alabama, Chicago, and Wisconsin, and Vanderbilt University Medical School also presented highlights of the research activities at their respective CNRU's.

The CNRU Directors also participated in the annual Conference of Federally-Supported Human Nutrition Research Units. That first conference, held on December 16-17, 1982, was sponsored by the Joint Subcommittee on Human Nutrition Research, and was described in detail in the FY 1983 Annual Report of the NIH Program in Biomedical and Behavioral Nutrition Research and Training. The proceedings of the conference were published in December 1984 under the title Federally Supported Human Nutrition Research Units: Selected Papers From the First Annual Conference. The second Conference of Federally Supported Human Nutrition Research Units and Centers was held January 14-15, 1985, in conjunction with the fifth annual meeting of CNRU directors.

In all of the CNRU's, nutrition is now being effectively integrated as a component of a broad spectrum of research projects that study the nutritional requirements throughout the life cycle and investigate the role of nutrition in cancer, cardiovascular diseases, diabetes, renal diseases, cystic fibrosis, digestive diseases, and osteoporosis, as well as in the management of patients with serious illness or injury. The CNRU's have begun to collaborate on joint research projects, on laboratory methods and services to standardize assays in order to obtain comparable results, and on education and outreach activities in order to increase the role of the CNRU's in nutrition education nationwide.

Each CNRU has made a commitment to provide training experiences in clinical nutrition for health professionals and young investigators at various levels. The presence of CNRU's at participating institutions has strengthened and enhanced nutrition education of both health professionals and the general public. Curriculum development in medical schools includes required and/or elective courses in basic and



advanced principles of nutrition sciences, independent study courses, special lectures, and preceptorships. The CNRU staffs also organize workshops and seminars, write and edit newsletters and pamphlets, and produce audiovisual and other kinds of information and materials in order to disseminate nutrition findings to physicians, other health professionals, and lay persons in the community.

One of the important outcomes of the CNRU's has been the increased visibility of nutrition programs, including opportunities for participation by medical students and fellows in research projects on nutrition problems, as well as the increased awareness of faculty of the appropriateness of a place for nutrition in the management of patients.

#### NUTRITION CONFERENCES SPONSORED BY THE NIH

Each year the NIH sponsors a number of conferences on a variety of nutrition topics that reflect the current interest of the Institutes in areas of program development for nutrition research and training. Such conferences also help to expedite the transfer of nutrition technology to scientists and educators so as to assure the appropriate application of research to practice. Table IV lists the 14 conferences held in FY 1984.

TABLE IV

## NIH SPONSORED NUTRITION CONFERENCES AND WORKSHOPS, FY 1984

<u>INSTITUTE</u>	<u>DATE</u>	<u>TITLE</u>
NCC	Oct. 2-4	Outpatient Management of Obesity (A Satellite Meeting of the 4th International Congress on Obesity)
NHLBI	Feb. 21-22	The Working Group to Discuss Strategies for Minimizing Coronary Heart Disease Among Blacks
NIADDK, NCI (US--Japan Mal- nutrition Panel)	Feb. 28-29	Vitamin A and Cancer Prevention
NHLBI, NCC NIA	Mar. 12-14	NIH Workshop on Nutrition and Hypertension
NIADDK, OMAR	Apr. 2-4	NIH Consensus Development Con- ference on Osteoporosis
FIC, NIADDK	May 2-4	International Conference on Biotin
NCI	May 17-18	Chemoprevention Clinical Trials: Problems and Solution
NHLBI	May 24-25	Nutrition in Sickle Cell Disease
NHLBI	June 6-7	The Lipid Research Clinics Coronary Primary Prevention Trial: Results and Analyses
NCI	June 7-8	Core Dietary Questionnaire
NIGMS	July 22-27	FASEB Summer Conference: Calcium and Cell Function
NICHD, NCI	Aug. 22-25	Methods for the Analysis of Human Milk
DRR	Sept. 11	Advances in Clinical Nutrition
NIADDK	Sept. 13-14	Structured Lipids and Their Use in Clinical Nutrition





**III.**

**FY 1984 OBLIGATIONS FOR  
NUTRITION RESEARCH AND  
TRAINING**



## DATA RETRIEVAL IN NUTRITION/HUMAN NUTRITION RESEARCH AND INFORMATION MANAGEMENT SYSTEM

In order to determine obligations for nutrition research and training, the Institutes' program staff reviews all research grants and contracts in accordance with the definition of nutrition research. Over 60 percent of the projects are 100 percent nutrition. For projects that are not 100 percent nutrition, the nutrition component is identified and the percentage of the overall project applicable to nutrition is then determined. The NIH has thus been able to eliminate such confusing and easily misunderstood terms as "primary/secondary," "major/minor," "nutrition related," and "direct/indirect" in referring to its nutrition program.

The analysis of the obligations of the NIH nutrition program is accomplished through the NCC office computerized data retrieval system that stores data on all the nutrition research and research training activities of the NIH. This data base is updated periodically and cross-checked against the NIH grant information and accounting system, IMPAC (Information for Management Planning, Analyses, and Coordination). This computer system has enabled the NCC office to carry out detailed analyses of the distribution by percentage of the nutrition component, support mechanism (contract, type of grant, etc.), and special interest areas. Other analyses are performed on an ad hoc basis.

Up through FY 1982, the NIH nutrition program was presented in terms of 15 special interest areas. Now, for the second year, the program is presented in accordance with the classification used by the Human Nutrition Research and Information Management (HNRIM) System. This system includes a computerized data base and data retrieval system that contains data on the nutrition research programs of the following Federal agencies: Department of Health and Human Services; U. S. Department of Agriculture; Veterans Administration; Agency for International Development; Department of Defense; and Department of Commerce-National Oceanic and Atmospheric Administration.

The classification categories used by the HNRIM system were originally developed by the Joint Subcommittee on Human Nutrition Research (JSHNR) to reflect the components included in the JSHNR definition of human nutrition research that was accepted by all the concerned Federal agencies in 1980. Nutrition projects included in the system are classified under five major areas: I. Research in the Biomedical and Behavioral Sciences; II. Research in Food Sciences; III. Research on Nutrition Monitoring and Surveillance of Populations; IV. Research in Nutrition Education; and V. Research on the Effects of Government Policy and Socioeconomic Factors on Food Consumption and Human Nutrition. Research in the Biomedical and Behavioral Sciences is subclassified under three major components: A. Research on Normal Nutritional Requirements Throughout the Life Cycle; B. Diseases and Conditions; and C. Nutrient Metabolism and Metabolic Mechanisms at the Cellular and Subcellular Levels. The system is subsequently divided into 34 categories. Each nutrition research project is assigned at least one of the 34 classifications, and as many classifications as



are needed are chosen in order to adequately identify all major nutrition aspects of the research activity being classified. The HNRIM classification system and the FY 1984 expenditures for each category are presented in appendix A. A narrative on the development of the HNRIM system can be found on pages 89-90.

#### FY 1984 OBLIGATIONS FOR NUTRITION RESEARCH AND TRAINING

In FY 1984, the total NIH actual obligation in biomedical and behavioral nutrition research and training was \$192,918,000. Actual obligations in nutrition by each Institute, DRR, and FIC are as follows:

NCI	\$50,119,000
NHLBI	44,553,000
NIDR	1,419,000
NIADDK	35,969,000
NINCDS	2,652,000
NIAID	1,646,000
NIGMS	2,271,000
NICHD	24,152,000
NEI	4,611,000
NIEHS	1,768,000
NIA	4,757,000
DRR	18,874,000
FIC	127,000.

Figure 7 presents the nutrition research and training obligations of each Institute, DRR, and FIC. The total nutrition obligation by Institute is represented by a bar divided into five segments. The lowest segment of the bar represents those grants and contracts with a nutrition component less than 50 percent of the entire grant or contract, followed by those with a nutrition component of 50 to 99 percent, and then those that are entirely (100 percent) nutrition research. The fourth segment represents training grants and fellowships, and the fifth segment represents intramural research obligations.

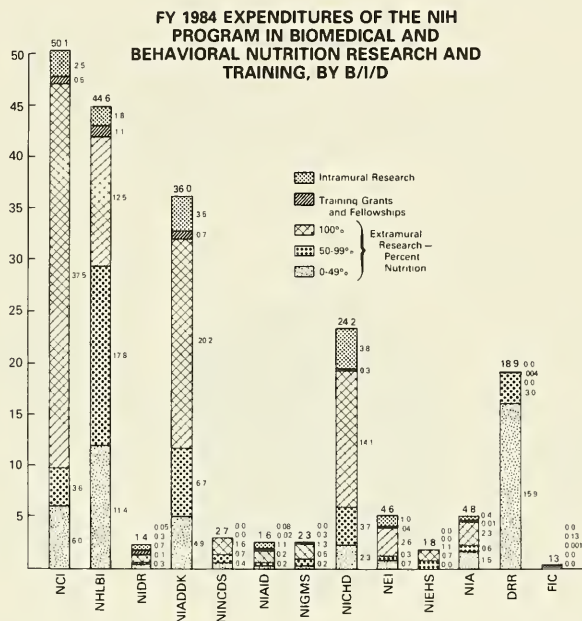
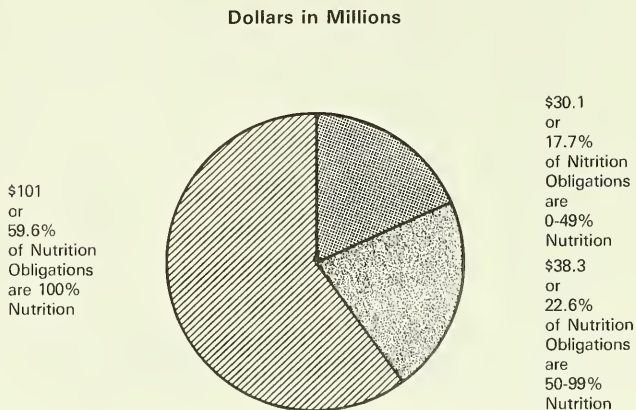


Figure 7

Figure 8 illustrates the extramural research support of the 11 Institutes and FIC, excluding DRR and nutrition training. About 60 percent of the funds are expended for projects that are entirely nutrition research; 23 percent are 50-99 percent nutrition; and the remaining 17 percent of the funds are for projects with less than 50 percent nutrition research. Between FY 1983 and FY 1984, the percentage of obligations expended for projects that are entirely nutrition increased from 57 to 60 percent, while obligations for projects less than 50 percent nutrition decreased from 21 to 18 percent. Thus, the majority of the NIH program in nutrition research consists of projects where the investigators are carrying out research that is devoted entirely to nutrition.

### FY '84 EXPENDITURES\* FOR NUTRITION GRANTS AND CONTRACTS



\*Excludes nutrition expenditures by DRR and for training.

Figure 8

Table V presents the FY 1984 nutrition obligations by category of support for the NIH as a whole, and appendix B contains the obligations for each Institute, DRR, and FIC (tables B-1 through B-13).

TABLE V

National Institutes of Health  
BIOMEDICAL AND BEHAVIORAL NUTRITION RESEARCH AND TRAINING, FY 1984,  
BY CATEGORY OF SUPPORT  
(Actual Obligations, in thousands of dollars)

	Item	Breakdown		Total	
		Number	Cost	Number	Cost
<u>Extramural</u>					
Research grants:	Regular . . . . .	1,255	89,274		
	Clinical trials . . . . .	150	12,600		
	Total . . . . .			1,405	101,874
Program projects:	Regular . . . . .	68	18,275		
	Clinical trials . . . . .	8	2,960		
	Total . . . . .			76	21,235
Contracts:	Regular . . . . .	80	13,161		
	Clinical trials . . . . .	17	1,716		
	Total . . . . .			97	14,877
Centers:	Regular . . . . .	62	13,827		
	Clinical trials . . . . .	1	64		
	Total . . . . .			63	13,891
Research Resources Support. . . . .				288	18,891
Reimbursement Agreements. . . . .				21	1,988
Research Career Development Awards. . . . .				85*	1,605
New Investigator Research Awards. . . . .				78*	2,219
Training:	Training grants . . . . .	341*	2,802		
	Fellowships . . . . .	35*	440		
	Total . . . . .			376*	<u>3,242</u>
Subtotal - Extramural . . . . .					\$ 179,822
<u>Intramural</u>					
Projects. . . . .				119	12,668
Training. . . . .				53*	<u>428</u>
Subtotal - Intramural . . . . .					\$13,096
TOTAL NUTRITION RESEARCH AND TRAINING - . . . .					\$ 192,918

\*Number of persons.

NOTE: The cost figures in this table reflect only research falling within the definition of nutrition research.

The extramural program is classified by mechanism of support into regular research grants, program projects, contracts, and centers. Clinical trials are funded by all four of these mechanisms. Research resources support, reimbursement agreements, research career development awards, new investigator research awards, and training grants and fellowships are also included in the extramural program. The intramural program consists of research projects and training (fellowships). In FY 1984, the actual obligations for extramural research, training, and manpower development accounted for \$179,822,000, while intramural research and training accounted for \$13,096,000. Descriptions of the extramural and intramural research and research training programs are provided in appendix C.

Research grants support a discrete, specified, circumscribed project performed by investigator(s) in areas representing specific interests and competencies. Such research is initiated entirely by investigators outside the NIH. In FY 1984, the NIH supported 1,405 research grants in nutrition for a total obligation of \$101,874,000. This category constitutes the largest single area of support in nutrition.

Program projects are also investigator initiated research, but differ from research grants in that they are awarded for the support of a broadly based, multidisciplinary, often long-term research program that has a specific major objective or a basic theme. A program project generally involves the organized efforts of relatively large groups, members of which are conducting research projects designed to elucidate various aspects or components of the major objective. In FY 1984, 76 program projects in nutrition were funded for \$21,235,000.

Contracts are initiated by the agency to develop or apply new knowledge or to test, screen, or evaluate a product, material, device, or component for use by the scientific community. In FY 1984, NIH funded 97 nutrition research contracts for \$14,877,000.

Centers are an additional component of agency initiated research that support any part of a full range of research and development from very basic to clinical. Centers may involve ancillary supportive activities, such as protracted patient care necessary to the primary research effort. The spectrum of activities comprises a multidisciplinary approach to a specific disease entity or biomedical problem area. In FY 1984, NIH obligations for the 63 centers with nutrition research activities were \$13,891,000.

Investigator initiated research (research grants and program projects) in FY 1984 amounted to \$123,109,000 (or 64 percent of all nutrition research and training obligations) whereas agency initiated research support in nutrition (contracts and centers) was \$28,768,000 (or 15 percent of nutrition research and training obligations). Thus direct support for nutrition research was predominantly investigator initiated.

Clinical trials in nutrition are supported by each of the four major mechanisms discussed above--research grants, program projects, contracts, and centers. A clinical trial is defined as a scientific



research activity undertaken to define the effect and value of prophylactic/diagnostic/therapeutic agents, devices, regimens, procedures, etc., applied to human subjects. The study must be prospective, and intervention of some sort must occur. The number of cases or patients depends on the hypothesis being tested, but must be sufficient to permit anticipation of a definite, statistically significant result. Phase I, feasibility, or pilot studies are excluded by definition.

FY 1984 obligations in support of 176 clinical trials involving nutrition totaled \$17,340,000. These obligations constitute 9 percent of total nutrition obligations for FY 1984. The distribution of clinical trials among the four support mechanisms is displayed in table VI.

TABLE VI  
SUPPORT MECHANISMS FOR CLINICAL TRIALS, FY 1984  
(in thousands of dollars)

<u>Funding Mechanism</u>	<u>Number of Clinical Trials</u>	<u>FY 1984 Expenditures</u>
Research Grants	150	12,600
Program Projects	8	2,960
Contracts	17	1,716
Centers	<u>1</u>	<u>64</u>
TOTAL	176	17,340

Research resources support is provided by the Division of Research Resources and NICHD. In FY 1984, \$18,891,000 was devoted to this category of the NIH nutrition program, with DRR expending \$18,870,000 through the following five mechanisms:

1. The General Clinical Research Centers Program, with nutrition obligations of \$15,101,588 in FY 1984, constitutes the bulk of DRR general research support. These centers foster the development of technological and therapeutic advances to expedite the application of basic biological knowledge into effective patient care.

The balance of \$3,768,412 is provided through the following four mechanisms:

2. The Animal Resources Program provides a unique institutional research environment for the use of nonhuman primates or other animals in multicategorical research.
3. The Biomedical Research Support Program responds to emerging research opportunities and allows the supported institution self-determination in the development and conduct of pilot and other small projects.

4. The Biomedical Research Technology Program attempts to interface the knowledge of the physical sciences, mathematics, and engineering with biology and medicine.
5. The Minority Biomedical Support Program provides funds to ethnic minority institutions to conduct research.

Reimbursement agreements are entered into between the NIH and other Federal agencies. In FY 1984, 21 such agreements were made in the area of nutrition by five Institutes, with total obligations of \$1,988,000. The reimbursement agreements are listed in table VII.

TABLE VII

INTERAGENCY REIMBURSEMENT AGREEMENTS WITH NUTRITION RESEARCH  
COMPONENTS FUNDED BY NIH IN FY 1984

## NATIONAL CANCER INSTITUTE

- o Chemoprevention of Epithelial Cancer by Retinoids (with Department of Energy at Brookhaven National Laboratory)
- o Research on Occupational Carcinogenesis (with National Institute of Occupational Safety and Health)
- o Epidemiological Studies of Cancer in Alaskan Natives (with Centers for Disease Control)
- o Procurement of Human Tissues (with U.S. Naval Medical Command)
- o Isotretinoin-Basal Cell Carcinoma Prevention Studies (5 agreements with U.S. Army and Naval Medical Commands)
- o Human Studies of Diet and Nutrition (with U.S. Dept. of Agriculture)

## NATIONAL HEART, LUNG, AND BLOOD INSTITUTE

- o Atherosclerosis Project--Nonhuman Primates (with DRR)
- o CDC Lipid Standardization Program (with Centers for Disease Control)
- o Services Provided to NHLBI for Nutrient Data (with U.S. Dept. of Agriculture)
- o Survey Data Performed by FDA on Coronary Primary Prevention Trial (CPPT) (with Food and Drug Administration)
- o Services Provided to NHLBI for Nutrient Composition Lab (with U.S. Agricultural Research Center)
- o Services Provided by USDA for Analysis of CPPT Study (with U.S. Agricultural Research Center)
- o International Food Composition Data System (with U.S. Dept. of Agriculture)

## NATIONAL INSTITUTE ON AGING

- o The NHANES I Epidemiologic Followup Survey (with National Center for Health Statistics)

## NATIONAL INSTITUTE OF ALLERGY AND INFECTIOUS DISEASES

- o Support of National Health and Nutrition Examination Survey (with National Center for Health Statistics)

## NATIONAL INSTITUTE OF CHILD HEALTH AND HUMAN DEVELOPMENT

- o Determinants of Infant Feeding Practices (with Health Resources and Services Administration)
- o Contraceptive Steroid Use from NHANES (with National Center for Health Statistics)

Research Career Development Awards (RCDA's) and New Investigator Research Awards (NIRA's) further manpower development in nutrition research. In FY 1984, 10 Institutes supported 163 individuals at a total cost of \$3,824,000 by these mechanisms. The description of the research supported by these awards is included in appendix C.

Eighty-five RCDA awards in nutrition were supported by NCI, NEI, NHLBI, NIA, NIADDK, NIAID, NICHD, and NIDR for a total obligation of \$1,605,000. The type and number of awards given are as follows:

- o "Research Scientist Development Awards" support scientists, who are committed to research and need advanced research training and additional experience (4 awards).
- o "Modified Research Career Development Awards" foster the development of young scientists with outstanding research potential for careers of independent research in the sciences related to health (27 awards).
- o "Research Career Awards" enable institutions to finance positions favorable to the intellectual growth and research productivity of established investigators of high competence for the duration of their careers (4 awards).
- o "Academic/Teacher Awards" create and encourage a stimulating approach to disease specific curricula that will attract high-quality students, foster academic career development of promising young teacher-investigators, develop and implement excellent multidisciplinary curricula through an interchange of ideas, and enable the grantee institution to strengthen its existing teaching program. The academic and teacher investigator awards are not used by all of the Institutes (38 awards).
- o "Clinical Investigator Awards" provide the opportunity for promising medical scientists (with demonstrated aptitude to develop into independent investigators) or faculty members to pursue research aspects of categorical areas applicable to the awarding unit, and aid in filling the important academic faculty gap in these shortage areas within health professional institutions of the country (10 awards).
- o "Physician Scientist Awards (Individual)" support a newly trained clinician nominated by an institution for the development of independent research skills and experience in a fundamental science (2 awards).

NIRA's are also used by the NIH as a mechanism for manpower development in nutrition. The NIRA encourages new investigators (including those who have interrupted early promising research careers) in basic or clinical science disciplines to develop their research activities within the program interests of NIH. This special grant-supported program provides funds to help bridge the transition from training status to that of established investigator. In FY 1984, 78 new investigator research awards were given for a total obligation of

\$2,219,000 by NCI, NEI, NHLBI, NIA, NIADDK, NIAID, NICHD, NIGMS, and NINCDS.

Training in biomedical and behavioral research is supported by NIH through national research service awards. Training grants are awarded to institutions; fellowships are awarded to individuals. In FY 1984, 341 extramural trainees in nutrition research were supported for a total of \$2,802,000, and 35 fellowships awarded for a total of \$440,000. Thus, total support for extramural training was \$3,242,000 for the 376 trainees and fellows. (See also table IX.)

Intramural nutrition research and training was carried out by eight Institutes with a total obligation of \$13,096,000 of which \$428,000 was devoted to training (fellowships) by two Institutes.

#### COMPARISON OF THE NUTRITION RESEARCH PROGRAM WITH THE OVERALL NIH RESEARCH PROGRAM

The entire NIH appropriation for FY 1984 was \$4,476,141,000 and the nutrition obligation was \$192,918,000. Thus, nutrition accounts for 4.3 percent of the total NIH budget. Support for nutrition research grants and program projects amounted to 5.2 percent of all NIH research grants and program projects, 4 percent of contracts, and 3.2 percent of centers. Research grants and program projects (investigator initiated research) constitute the major part of NIH support. Table VIII compares the total NIH and nutrition obligations in three major components of extramural research.

TABLE VIII

#### COMPARISON OF TOTAL NIH AND NUTRITION OBLIGATIONS IN THE THREE MAJOR COMPONENTS OF EXTRAMURAL RESEARCH, FY 1984 (in thousands of dollars)

	NIH Total		Nutrition Program	
Research grants and program projects	2,389,553 (75%)		123,109 (81%)	
Contracts	344,642 (11%)		14,877 (10%)	
Centers	<u>428,373</u> (14%)		<u>13,891</u> ( 9%)	
TOTAL (of the three components)	3,162,568 (100%)		151,877 (100%)	



As can be seen from table VIII, research grants and program projects account for 75 percent of the NIH extramural research component and 81 percent of the nutrition budget. Contracts represent 11 percent for NIH and 10 percent of the nutrition program, while centers represent 14 percent for NIH as a whole and 9 percent for the nutrition program. Thus, investigator initiated research is the predominant component of both the agency and the nutrition program with such research comprising a larger percentage of the nutrition program than that of the NIH programs overall. With respect to centers, the nutrition program lags behind the NIH programs as a whole which can be explained in part by administrative accounting changes in support mechanisms for the Clinical Nutrition Research Unit program; the five CNRU's supported by NIADDK are considered centers whereas the two CNRU's supported by NCI are considered program projects.

# NUTRITION RESEARCH TRAINING

The NIH supports training in biomedical and behavioral nutrition research in both the extramural and the intramural programs. Table IX shows the type and number of persons trained and the expenditures in FY 1984.

TABLE IX  
NIH TRAINING IN NUTRITION, FY 1984

<u>Institute</u>	<u>M.D. Degree</u>	<u>Ph.D. Degree</u>	<u>Other Degree*</u>	<u>Pre-Doc</u>	<u>Total Number of Persons Trained</u>	<u>FY 1984 Obligations (in thousands of dollars)</u>
<u>EXTRAMURAL:</u>						
<u>Institute Training Grants</u>						
NCI	10	25	2	45	68	455
NHLBI	49	86	3	0	138	994
INIDR	0	3	7	0	10	233
NIADDK	7	10	0	24	41	617
NIAD	4	0	0	0	4	7
NIGMS	8	0	0	2	10	208
NICHD	10	7	1	4	22	280
NIA	0	0	0	32	32	4
IDRR	<u>0</u>	<u>0</u>	<u>0</u>	<u>2</u>	<u>2</u>	<u>4</u>
Subtotal	88	131	13	109	341	2,802
<u>Individual Fellowships</u>						
NHLBI	1	5	0	0	6	68
INIDR	0	1	1	0	2	20
NIADDK	1	4	1	0	6	96
NIAD	2	0	0	0	2	18
NIGMS	1	0	0	0	1	0
NICHD	1	11	0	0	12	62
NEI	0	1	1	0	2	41
NIA	0	1	0	0	1	9
FIC	<u>3</u>	<u>0</u>	<u>0</u>	<u>0</u>	<u>3</u>	<u>126</u>
Subtotal	9	23	3	0	35	440
EXTRAMURAL SUBTOTAL	97	154	16	109	376	3,242
<u>INTRAMURAL</u>						
NHLBI	12	0	0	0	12	93
NIADDK	8	5	0	0	13	335
NICHD	<u>11</u>	<u>10</u>	<u>7</u>	<u>0</u>	<u>28</u>	<u>0</u>
INTRAMURAL SUBTOTAL	31	15	7	0	53	428
NIH TRAINING TOTAL	128	169	23	109	429	3,670

\* Other Degree includes M.D./Ph.D, Ph.D./D.D.S., D.D.S, D.V.M., D.Sc., etc.

Within the extramural program, two basic mechanisms are used for nutrition training support: institutional awards and individual awards.

The institutional national research service awards, commonly called "training grants," are designed to enable institutions to make training awards to individuals selected by them for predoctoral and postdoctoral research training.

In FY 1984, out of the total NIH expenditure of \$137,307,000 to train 8,908 full-time equivalent persons, \$2,802,000 was expended to train 341 persons in nutrition. Thus, nutrition training accounted for 2.0 percent of the total NIH training expenditure and 3.8 percent of the total trainees supported.

The postdoctoral individual national research service awards, called "fellowships," are awarded to provide postdoctoral research training to individuals to broaden their scientific background and extend their potential for research. Out of the total NIH expenditure of \$29,155,000 to support 1,606 fellows in FY 1984, the nutrition program expended \$440,000 to support 35 fellows. Thus, nutrition fellowships accounted for 1.5 percent of the total NIH expenditure for fellowships and 2.2 percent of the total NIH supported fellows.

Combining training grants and fellowships, \$3,242,000 was expended to support the 376 persons trained in nutrition in FY 1984. The nutrition expenditure accounted for 2.0 percent of the total NIH training expenditure and the number of trainees in nutrition accounted for 3.5 percent of the total NIH trainees.

Within the NIH intramural program, three Institutes, NHLBI, NIADDK, and NICHD, supported nutrition training of 53 scientists at an obligation of \$428,000 in FY 1984.

Descriptions of the research carried out by both the extramural and intramural trainees are included in appendix C.

TABLE X

COMPARISON OF TOTAL NIH AND NUTRITION PROGRAM SUPPORT OF EXTRAMURAL  
RESEARCH TRAINING AND FELLOWSHIPS, FY 1978 - FY 1984  
(in thousands of dollars)

FY	Total NIH				Nutrition Program			
	Training		Fellowships		Training		Fellowships	
	Number of Trainees	\$	Number of Fellows	\$	Number of Trainees	\$	Number of Fellows	\$
1978	9,260	117,581	1,863	26,345	130	1,956	39	463
1979	9,204	116,193	1,993	27,468	261	2,555	36	466
1980	8,878	141,719	1,786	34,669	284	3,201	51	628
1981	9,121	144,719	1,574	30,897	268	3,159	36	549
1982	8,867	123,407	1,539	27,067	307	2,419	38	415
1983	8,963	135,152	1,607	29,502	377	3,056	34	391
1984	8,908	137,307	1,606	29,155	341	2,802	35	440

Table X shows that whereas the number of trainees and the financial support for NIH as a whole remained relatively constant from 1978 through 1983, the number of trainees in the nutrition program doubled between 1978 and 1979, remained relatively constant until 1982, and has since increased slowly. Over the 7-year period, the number of nutrition trainees reached its highest level in FY 1983, and has decreased by 10 percent in FY 1984 with 341 trainees being supported.

There was a small increase in the number of NIH fellowships in FY 1983 which was maintained in FY 1984; the number of fellowships in nutrition has remained relatively constant over that period.







**IV.**

**COORDINATION OF NUTRITION  
RESEARCH AT THE NIH**



## NUTRITION COORDINATING COMMITTEE AND SUBCOMMITTEES

The NCC, established in 1975, operates out of the Office of the Director and is advisory to the Director, NIH. The membership of the NCC consists of representatives from 11 Institutes, Fogarty International Center, Division of Research Resources, and Division of Research Services. Additional NIH offices and other agencies of the Department of Health and Human Services have liaison representatives to the committee. As of September 30, 1984, the NCC was composed of the chairman, 22 members and alternates, 8 liaison representatives and alternates from interested offices within the NIH, and 10 liaison representatives and alternates from other agencies within DHHS (see roster on pages vi-vii).

The mandate of the NCC is to review, stimulate and encourage the necessary support of nutrition research and training in order to better define the role of nutrition in the promotion of health, and the prevention and treatment of disease.

In FY 1977, the NCC developed the "Nutrition Policy of the NIH" and the "Definition of Nutrition Research at the NIH," which are still used by the NCC today. Each year, the NCC reviews and comments on the plans, execution, and results of pertinent Bureau, Institute, and Division research efforts relating to nutrition in order to develop the Annual Report of the NIH Program in Biomedical and Behavioral Nutrition Research and Training.

The NCC meetings are normally held once a month and are attended by the members, liaison representatives, and committee office staff. In addition to the regular business of the committee, special presentations on subjects of current interest to the NCC are frequently made by scientists from other agencies or professional groups such as the American Medical Association and American Institute of Nutrition, etc. The NCC meetings are followed by scientific seminars in nutrition in order to highlight or review research advances in nutrition. The seminar speakers include NIH grantees from the academic community as well as intramural scientists of the NIH and other Federal agencies.

The NCC office receives, analyzes and coordinates the many aspects of nutrition research and training at the NIH. The office staff provides information on the NIH nutrition research program and on various topics of nutrition research to a broad spectrum of sources such as the Congress, the Executive branch, including various agencies of the Public Health Service, the scientific community and the public. Activities of the NCC office are described in detail in section VI of this report.

The mandate of the NCC, the charges of the Program Subcommittee and the Subcommittee on Nutrition Education, the Nutrition Policy of the NIH, and the Definition of Nutrition Research follow.

## MANDATE OF THE NUTRITION COORDINATING COMMITTEE

### The Nutrition Coordinating Committee:

- o Reviews and comments on the plans, execution, and results of pertinent Bureau, Institute, and Division research efforts relating to nutrition in order to develop the Annual Report of the NIH Program in Biomedical and Behavioral Nutrition Research and Training.
- o Processes and responds to incoming requests for nutrition information from the DHHS and other Federal agencies, the Executive Branch of the Government, the Congress, outside institutions, and the public.
- o Maintains up-to-date information on funding and on intramural and extramural research and training activities in nutrition.
- o Develops and monitors means for improving the coordination of these activities.

Within the scope of the major activities described above, the NCC has the following specific functions:

- o To define nutrition research at the NIH. (Accomplished, see page 75.)
- o To develop a policy statement for research and training in nutrition at the NIH. (Accomplished, see page 73.)
- o To establish information exchange. Each representative presents to the NCC any new plans, activities, conferences, and workshops that are concerned with nutrition. Future workshops and conferences are discussed to ensure full participation of all relevant Institutes; when many Institutes are involved, the NCC sponsors or cosponsors such workshops or conferences. Through the information exchange mechanism, the NCC identifies areas of collaboration for further research. The NCC informs the NIH nutrition community of all meetings, both within and outside NIH, concerned with nutrition. The committee, if requested, also reviews and comments on nutrition reports generated by the NIH and by other Federal and non-Federal agencies.
- o To develop a data retrieval system for research and training in nutrition. (Accomplished, see page 53.)
- o To review proposed legislation and regulations. The NCC develops mechanisms for receiving, reviewing, and distributing information on proposed legislation affecting nutrition policy.
- o To develop and maintain effective liaison with other departments and agencies that have nutrition activities. The NCC assesses existing liaison mechanisms and identifies those departments and agencies requiring a liaison relationship. Liaison representatives provide information to the NCC.

- o To encourage the application of nutrition research to practice. The NCC members identify research data that are ready for "technology transfer" and promote the appropriate application of new knowledge in nutrition.
- o To promote the dissemination of information for the purpose of public education on the role of nutrition on health and disease. The NCC assists in coordinating Bureau, Institute, and Division efforts in nutrition education and acts as a focal point for the dissemination of nutrition information to the public.

#### CHARGE OF THE PROGRAM SUBCOMMITTEE

- o To develop joint program announcements
- o To consider nutrition conferences
- o To discuss the advisability of outside speakers for the scientific seminars at the NCC meetings.

#### CHARGE OF THE SUBCOMMITTEE ON NUTRITION EDUCATION

- o To review NIH nutrition publications designed for the public
- o To develop public service announcements
- o Develop and implement National Nutrition Month activities at NIH.

#### NUTRITION POLICY OF THE NIH

##### Policy Objectives

The NIH supports DHHS policy by sponsoring and conducting biomedical research designed to improve the quality of life for all Americans through optimal nutrition. Basic biomedical nutrition research will develop knowledge needed to promote and maintain health, as well as to prevent and treat disease.

Nutrition research has passed through two stages and is now entering a third. The first stage saw the discovery of vitamins and the development of many of the basic nutritional requirements. The second stage reduced nutrition to subcellular and molecular terms within areas of biochemistry and physiology. The third stage calls for a synthesis of newer findings for translation into practical information to assist the individual to develop normally, to avoid disease, and to live as long and as healthy a life as possible. For this third stage, knowledge is needed that will permit distinction among individuals in terms of genetic differences that affect dietary requirements.

##### Areas of Emphasis



Current nutrition research at NIH concentrates on eight critical areas:

1. Clinical Nutrition Throughout the Life Cycle. Research in this initial area examines variations in nutritional requirements to promote and maintain health during all phases of the life cycle. Within the clinical nutrition program, research is also directed towards elucidating the effects of infant feeding practices and infant nutrition on subsequent physiological, immunological, and mental development. Another research goal involving the life cycle is to understand the effects of maternal nutritional status and maternal diet before and during pregnancy on the development of the fetus. In order to understand the ramifications of this nutritional problem, more must be learned about the interaction between the genetic makeup of an individual and his dietary intake. Special emphasis is given to studies on the role of nutrition in health of the aged and aging process, particularly the effects of aging on nutrient utilization, digestion, absorption, and metabolism, and nutrition and age-related mental deterioration.
2. Role of Nutrition in Disease Development. The NIH conducts research on mechanisms by which dietary deficiencies, imbalances, and excesses lead to the development of physical and mental diseases and disorders.
3. Prevention of Disease. The NIH has assumed a leading role in shifting the emphasis in nutrition research from curing disease after symptoms have developed to preventing or delaying the onset of disease. Continued research emphasis is given to malnutrition in all its guises, including under- and overnutrition, obesity, food faddism, and specific dietary deficiencies.
4. Treatment of Disease. The NIH develops nutritional therapies for specific diseases such as cancer, gastrointestinal disorders, obesity, osteoporosis, renal insufficiency, atherosclerosis, and inborn errors of metabolism. Improved methods are being developed to provide general nutritional support for newborns of low birth weight who may require parenteral supplementation and for elderly, disease-ridden, traumatized, or postoperative patients who may require total parenteral nutrition or elemental diets.
5. Technology Transfer. An important component of the NIH nutrition policy is to assure appropriate application of research in practice. To expedite transfer of nutrition technology, the NIH is establishing mechanisms to evaluate research data relevant to nutrition and public health.
6. Nutrition Education. The NIH continues to support research in nutrition education as byproducts of clinical trials and demonstration projects; by the education of the physician through professional societies, scientific meetings, and journals; and by the production of nutrition education materials for the health educator and the public. Encouragement of positive nutrition behavior is an obvious task for educators of children, young adults, and the

elderly.

7. Research Training. The NIH encourages and supports the teaching of modern biochemical nutrition at the pre- and postdoctoral levels. This training includes the disciplines upon which nutrition research is based such as gastroenterology, endocrinology, metabolism, developmental biochemistry, genetics, and molecular biology. The NIH also promotes expanded training programs in basic and clinical nutrition research aimed principally at the physician investigator and clinically oriented biomedical scientists.
8. Coordination. The NIH cooperates in establishing mechanisms for interagency coordination. Nutrition research at the NIH is coordinated through the Nutrition Coordinating Committee. Institutes initiate their own nutrition programs within their appropriated budgets. The committee seeks agreement on critical issues of definition, comments upon individual programs identified to it, maintains an information exchange (mechanisms for program development), promotes liaison with other Federal agencies, and encourages coordinated program planning among Institutes and with other appropriate agencies. The committee assists in the development of nutrition data retrieval systems, and reviews legislative and regulatory initiatives that impact upon human nutrition research.

#### DEFINITION OF NUTRITION RESEARCH AT THE NIH

Included in the first report of the NIH Program in Biomedical and Behavioral Nutrition Research and Training, FY 1977, issued by the NCC, was the definition of biomedical and behavioral nutrition research that the NCC developed. That definition, which continues to serve as a basis for data retrieval and for the assessment of information about the nutrition research and training activities of the NIH, is as follows:

"The term nutrition research includes studies designed to assess the consequences of food or nutrient intake and utilization in the intact organism, including man, and the metabolic and behavioral mechanisms involved. These studies encompass investigation of nutrient variables at the cellular or subcellular level. This definition also includes:

- o Research designed to elucidate the metabolic role or function of nutrients in both animal models and man.
- o All studies concerned with genetic-nutrient-environmental interactions where a nutrient is a variable.
- o Dietary studies expected to produce significant changes in health status, including the maintenance of health and the treatment of disease in man. Such studies might include clinical trials, epidemiological studies, metabolic studies, surveillance, and nutritional status monitoring studies."





**V.**

**ACTIVITIES AND ACCOMPLISHMENTS  
OF THE NUTRITION COORDINATING  
COMMITTEE AND SUBCOMMITTEES**



## NUTRITION COORDINATING COMMITTEE

Many of the activities of the NCC and its two subcommittees (the Program Subcommittee and the Subcommittee on Nutrition Education) involve the transfer of the latest scientific information on various areas of nutrition research to members of the scientific community, the Congress, and the general public. Such activities help to provide the most recent scientific information on specific topics of research interest, to promote additional research in specific areas, and to alleviate confusion on nutrition topics of current debate.

Each year as part of the monthly NCC meetings, scientific seminars are presented by prominent scientists working in areas of nutrition research of current interest to the NCC members. In FY 1984, the 10 seminars covered such topics as mechanisms of food-induced behavioral reaction, animal models for human nutrition research, the effect of exercise on food intake, parental factors in childhood weight control, HNRM system, prevention of blindness, psychology and physiology of obesity, dietary protein and the incidence of cerebral lesions in stroke prone rats, international network of food data base systems, and international nutrition research. Each of the seminars provided insight on the most recent scientific advances in the area of interest. A detailed description of each seminar presented in FY 1984 may be found in appendix I.

### "Eat Well, Be Well" Videotape Series and Cookbook

Following the wide public and professional acceptance of the first "Eat Well, Be Well" series, beamed in March 1981 to 225 Public Broadcasting System (PBS) television stations across the country, the NCC again agreed to serve as consultants in a second production, "Eat Well, Be Well II." The second series was also produced by Amram Nowak Associates with funds from the Metropolitan Life Foundation.

"Eat Well, Be Well II," beamed by satellite in July 1983 to all PBS television stations, consists of 14 7-minute videotape segments that explain the role of nutrition in health promotion and disease prevention with nine segments featuring prominent physicians. One segment features former DHHS Secretary Richard S. Schweiker explaining the importance of a regular exercise routine to health promotion. The series also includes a segment on "Body Weight," a segment by an Illinois farmer speaking on the production of low-fat meat, and an ethnic program with people of various backgrounds displaying the foods they commonly eat. Other segments address the issues of vitamins and minerals, carbohydrates, prenatal diets, milk and dairy products (and their relationship to osteoporosis), dieting, alcohol, fiber, vegetarianism, food substitution and cholesterol. Helen Hatton, home economist and chef in the "Eat Well, Be Well" series is again featured demonstrating appropriate recipes for the various nutrition topics. The theme song of the series emphasizes the role of proper nutrition and exercise in maintaining health. The series illustrates the successful collaboration of industry, government, and the scientific community in promoting public health.



In FY 1984, the videotapes accompanied the "NIH-NCC Nutrition Research Exhibit" to a number of scientific and organizational meetings and health fairs, and were also shown as part of National Nutrition Month Activities at the NIH. The series, which is now also available on 16mm sound film, can also be used for nutrition instruction in primary and secondary schools, by church groups, and by any group interested in the role of nutrition in health and disease.

Planning for the production of "Eat Well, Be Well III," which will provide nutrition information to young children, has begun with Amram Nowak Associates, Metropolitan Life Insurance Company, the American Academy of Pediatrics, and the NCC. Filming is scheduled to begin in FY 1985.

Another project underway by Metropolitan Life Insurance Company is publication of the "Eat Well, Be Well Cookbook." The NCC Chairman wrote the introduction to the book and assisted in the preparation. The cookbook will include some of the recipes from both "Eat Well, Be Well I and II," as well as additional recipes consistent with the DHHS/USDA pamphlet "Nutrition and Your Health, Dietary Guidelines for Americans." Plans are for the cookbook to be published in 1985.

#### Conferences Sponsored by the NCC

The NCC mandate calls upon the NCC to sponsor conferences, workshops, and symposia in areas of nutrition research that are of concern to the Institutes. In FY 1984, the NCC participated actively in the development of two conferences:

- o "Outpatient Management of Obesity," a satellite meeting of the 4th International Congress on Obesity, held October 2-4, 1983, in Bethesda, Maryland. This conference was one of the six satellite conferences held in conjunction with the "Fourth International Congress on Obesity" held October 5-8, 1983, in New York City. The NCC Chairman attended several planning meetings and cochaired the satellite meeting. The following issues were addressed at the satellite meeting: goals of treatment of obesity; programmatic factors (physiological and psychological) of obesity; assessment of motivation and compliance; integration of treatment modalities for obesity; characteristics of professional weight control programs; standards for professional weight loss clinics; cost:benefit analysis of outpatient management of obesity; third-party reimbursement for treatment of obesity; policy issues; and trends in research related to the management of obesity.
- o The "NIH Workshop on Nutrition and Hypertension" held March 12-14, 1984, in Bethesda, Maryland, and cosponsored by the NCC, NHLBI, and NIA, was the annual NCC nutrition conference for FY 1984. The importance of research on nutrition and hypertension was defined as twofold: 1) In spite of steady progress over the past several years toward understanding the mechanisms of blood pressure regulation and the pathogenesis of hypertension, the role of nutritional influences on these processes remains

unclear and requires extensive investigation; and 2) because the majority of patients with elevated blood pressure fall in the borderline and mild hypertensive categories, the need to support research on nonpharmacologic strategies for the management of these patients has become increasingly apparent. Nutritional interventions are likely to play a major role as possible strategies.

The workshop consisted of two major activities: presentation of position papers on selected dietary nutrients for which there is evidence to suggest that they have an influence on blood pressure, and working group sessions devoted to the specification of research objectives relative to the material presented in the position papers. The position papers, in addition to touching on an overview of hypertension and nutrition research methods, expounded on the roles of sodium and other electrolytes in hypertension; calorie intake, obesity and hypertension; dietary proteins, amino acids, carbohydrates, alcohol, trace metals, and hypertension; dietary fats, prostaglandins, and hypertension; and nutritional considerations of special populations, including the young and the elderly. The working groups, similarly organized, delineated short- and long-term research objectives for advancing science in nutrition and hypertension.

The workshop participants concluded that: 1) no specific diet recommendations to prevent hypertension in the general population can be made at this time; 2) a modest restriction of salt was not considered harmful, and would be helpful for reducing hypertension in the salt-sensitive individual; and 3) screening the population to identify the salt-sensitive individual requires serious consideration. The proceedings of the workshop were published in 1985.

#### PROGRAM SUBCOMMITTEE

In accordance with its charge, the Program Subcommittee developed two joint program announcements: (1) "Studies on Obesity," cosponsored by NCI, NHLBI, NIADDK, NIA, NICHD, and NINCDS, and NIAAA, NIMH, and NIDA of ADAMHA, and (2) "Core Grants for Clinical Nutrition Research Units" cosponsored by NCI, NIA and NIADDK. Descriptions of both program announcements are given on pages 271 and 275 of this report.

The subcommittee members were also instrumental in the planning of the two nutrition conferences noted on the preceding page, and participated in the planning meeting for the joint conference on the "Health Effects of Polyunsaturated Fatty Acids in Seafoods." This conference, which is scheduled for June 24-26, 1985 in Washington, D.C., will be cosponsored by the NCC; the National Marine Fisheries Service, National Oceanic and Atmospheric Administration, Department of Commerce; and the National Fisheries Institute. The objective of the conference is to develop a research agenda to determine the spectrum of the health effects of polyunsaturated fatty acids of

seafood origin in the American diet. The conference will consist of review papers and presentations of current research and will be cochaired by the NCC Chairman.

Throughout the year, the Subcommittee members have also provided input important for the development of NIH responses to a number of nutrition activities under way at the Department such as the proposed Surgeon General's Report on Nutrition and the DHHS 5-Year Plan for Nutrition Research.

#### SUBCOMMITTEE ON NUTRITION EDUCATION

In FY 1984, in accordance with its charge and the "Guidelines for Review of NIH Nutrition Publications for the Public" (Appendix J), the Subcommittee on Nutrition Education reviewed the following nutrition publications intended for the public: Good News, Better News, Best News...Cancer Prevention and Diet, Nutrition and Cancer Prevention: A Guide To Food Choices, developed by NCI; Age Page--Nutrition, A Lifelong Concern and Age Page--Hints for a Healthy Diet, developed by NIA; The Truth About Dietary Fiber, developed by NIADDK; and Facts About Blood Cholesterol and Facts About Obesity: An Independent Risk Factor for Heart Disease, developed by NHLBI.

If requested by an Institute, the subcommittee members also review nutrition pamphlets intended for specific patient populations. In FY 1984, the subcommittee reviewed the pamphlet Epidermolysis Bullosa developed by NIADDK, which contains specific nutrition information for this patient population.

Fact sheets developed as part of the "NIH-NCC Expanded Foods for Health Program" were reviewed and finalized by the subcommittee members with input from the various Institutes. They include: "Facts About Obesity," developed by NIADDK; "Heart Healthy Habits" and "What You Eat May Help Control High Blood Pressure," developed by NHLBI; "Sugar and Tooth Decay," developed by NIDR; and "The Reasons to Breastfeed," developed by NICHD.

The subcommittee is continuing its work with the GSI Cafeteria Service, through the NIH area manager, to introduce more nutritious food selections as part of the regular NIH cafeteria service. The GSI Cafeteria Service at NIH continues to feature the "Eat Well, Be Well" salad bar complete with the calorie counts of the various salad toppings at a number of the NIH cafeterias. In addition, the subcommittee also provided input to the Recreation and Welfare (R&W) Association at the NIH regarding the scientific accuracy of the various diet programs offered to NIH employees under their aegis.

In order to avoid duplication of effort and enhance the quality of the nutrition education materials destined for the public, the subcommittee continues to work closely with the nutrition education staff of the CNRU's to collect nutrition materials prepared by the CNRU's and to provide the CNRU directors and staff with information on nutrition publications and resources available from NIH and other agencies within the DHHS.



### National Nutrition Month at the NIH, March 1984

For the fourth consecutive year, activities to commemorate National Nutrition Month were held on the NIH campus during March 1984. The NCC and the Subcommittee on Nutrition Education cosponsored these activities, with the cooperation of the R&W, the Occupational Medical Service (OMS), the GSI Cafeteria Service, and the NIH Fitness Center.

Since 1984 was the year of the Olympic games, activities for National Nutrition Month at the NIH emphasized the theme "Nutrition and Exercise--Team Up for Good Health...the Olympic Way." The theme was displayed on posters featured in all of the NIH cafeterias, the Information Offices of the Institutes, the ACRF Visitor's Center, and the National Library of Medicine. The activities featured throughout the month included scheduled viewings by the OMS of two "Eat Well, Be Well II" segments: "Body Weight and Health" and "Cholesterol."

Four special lecture presentations were given during the month:

- o "Prevention of Coronary Heart Disease Through Cholesterol Lowering" by Dr. Basil Rifkind, chief, Lipid Metabolism/Atherogenesis Branch, NHLBI
- o "Nutritional Factors in Hypertension" by Dr. Norman Kaplan, professor of internal medicine, Head of Hypertension Division, University of Texas Southwestern Medical School
- o "Total Fitness and Joy" by Dr. George Sheehan, author and well-known sports philosopher
- o "Exercise and Weight Control" by Janet Vizard, director, and Tom Klein, associate director of the NIH Fitness Center.

In order to emphasize the importance of a regular exercise routine and provide employees with some idea as to the various exercise programs available through the Fitness Center, coed class demonstrations of the "Quik Fit" program were offered. This program, open to employee participation, featured cardiovascular exercises with stretching and strengthening.

The GSI Cafeteria Service included a number of National Nutrition Month Specials of the Day, and continued to provide NIH employees with nutrition information on the calorie and sodium counts of various food items as well as the "Eat Well, Be Well" salad bar complete with 12 topping choices.

Also during March, the NIH-NCC Nutrition Research Exhibit and its accompanying pamphlet, Nutrition Research at the National Institutes of Health, were displayed at the Visitors Center of the ACRF. Plans are under way to display the exhibit in the ACRF on a permanent basis when it is not traveling to the various scientific meetings.

## NIH-NCC Nutrition Research Exhibit

In FY 1984, the NIH-NCC Nutrition Research Exhibit was displayed and enthusiastically received at four major scientific meetings and numerous health fairs. The development of the exhibit was a major accomplishment of the NCC and the Subcommittee on Nutrition Education in FY 1983. NCI, NHLBI, NIDR, NIAID, NIGMS, NICHD, DRR and the NCC office provided financial support for this activity.

The freestanding exhibit, designed to be displayed at scientific meetings and health fairs, provides the scientific community, health professionals, interested consumers, and the general public with information on the NIH nutrition program. The exhibit illustrates the transfer of nutrition research from basic laboratory studies to clinical research, and the ultimate education of individuals on the role of nutrition in health promotion, disease prevention and disease treatment.

The exhibit's pamphlet, entitled "Nutrition Research at the NIH," provides descriptive information on the nutrition research programs of the 11 NIH Institutes and DRR, the names and addresses of the contact persons for the nutrition program within each Institute and DRR, as well as information on the application and review process for grants, projects, and training.

The NIH-NCC Nutrition Research Exhibit serves to illustrate the NIH commitment to nutrition research; helps to stimulate nutrition research along the lines of individual Institutes' program interests; and helps to encourage high quality applications for research projects in basic research, clinical investigation, and in the epidemiological aspects of nutrition science.

The meetings where the exhibit was displayed in FY 1984 included: the annual meetings of the Federation of American Societies for Experimental Biology (FASEB), held in St. Louis, Missouri; the American Society of Clinical Oncology (ASCO), and the American Association for Cancer Research (AACR), held in Toronto, Canada; and the 9th International Congress of Dietetics held in Toronto, Canada. In addition, the exhibit along with the "Eat Well Be Well II" videotapes was featured at the second annual "Health and Fitness Days" of the Department, held at the Hubert Humphrey Building in Washington, D.C., and at a variety of health fairs, including those held at the University of Maryland, the Department of Treasury, the Federal Employee Management Agency, and the General Accounting Office.



**VI.**

**ACTIVITIES OF THE NUTRITION  
COORDINATION COMMITTEE OFFICE**





As in past years, in addition to staffing the NCC and its subcommittees, the NCC office responded to a great number and variety of information requests on nutrition, nutrition research, and the NIH Program in Biomedical and Behavioral Nutrition Research and Training from a broad spectrum of sources, such as Congress and the Office of Technology Assessment; various agencies of the Public Health Service; and the scientific community and the public, both nationally and internationally. The central focus provided by the office has greatly facilitated NIH responses.

#### CONGRESSIONAL HEARINGS ON NUTRITION

In FY 1984, the NCC office staff provided input and was present at the hearing on the "National Nutrition Monitoring and Related Research Act of 1984, H. R. 4684," held on June 20, 1984, before the Subcommittee on Science, Research and Technology of the House Science and Technology Committee and the Subcommittee on Department Operations, Research and Foreign Agriculture of the House Agriculture Committee. This was the fourth annual oversight hearing on nutrition research and related areas held jointly by the two subcommittees. The hearing focused on the purpose and proposed components of H. R. 4684. The Assistant Secretary for Health, DHHS, testified at the hearing on the Department's views on the bill and also presented status reports on: 1) the Department's FY 1984 activities in nutrition monitoring; 2) the Clinical Nutrition Research Unit program; 3) the Human Nutrition Research and Information Management System; and 4) the 5-Year Federal Human Nutrition Research Plan. The NCC Chairman attended the hearing as the NIH representative and responded to questions.

With regard to the CNRU program, the Assistant Secretary stated:

"The establishment of seven CNRU's by NIH was a creative and imaginative response to a long-standing need to bring clinical nutrition into the mainstream of clinical research and practice...The CNRU program of NIH, now in its fifth year, has been very successful in strengthening a multidisciplinary research program in clinical nutrition and in improving the education programs in nutrition for medical students and other health professionals in each of the participating institutions. In addition, the CNRU program has provided support for the training of new clinical investigators in nutrition and for the development of nutrition education materials for patients and the general public."

In referring to the HNRIM system, the Assistant Secretary noted that from the reports of those who have had an opportunity to use the system, all have expressed great satisfaction with its operation and the utility of its output.

## OFFICIAL REPORTS AND SPECIAL PRESENTATIONS ON NUTRITION

The NCC office provides information on the DHHS and/or NIH nutrition research activities for inclusion in reports prepared by the General Accounting Office, as well as reports prepared by other Federal agencies. In addition to numerous special reports, the NCC office annually supplies data used in the publication NIH Extramural Programs, which is a compendium of the scientific programs of the NIH components that award grants, cooperative agreements and contracts. The "Program in Biomedical and Behavioral Nutrition Research and Research Training" is included in the section of the report on "Trans-NIH Research Programs."

The NCC Chairman and office staff receive a growing number of invitations each year from professional societies and other national and international groups interested in nutrition to present the NIH nutrition program or make special presentations on nutrition. In FY 1984, the NCC Chairman made presentations to the Environmental, Occupational, and Nutritional Health Committee of the Medical Society of the District of Columbia; the National Nutrition Consortium's Public Affairs Update on "Food, Nutrition, and Your Government"; the FASEB annual meeting; the American Society for Clinical Nutrition's "Conference on Clinical Nutrition Fellowship Training for Physicians"; and the Annual Congressional Breakfast sponsored by the National Fish Meal and Oil Association. International meetings where the NCC Chairman also made presentations included the 9th International Congress on Dietetics in Toronto, Canada; the Group of European Nutritionists' "Workshop on Nutritional Status Assessment of Individuals and Population Groups" in Athens, Greece; and the Cavendes Foundation Symposium on the Challenge of Food and Nutrition in the Promotion of Health and National Development in Caracas, Venezuela. As a result of the presentation made in Venezuela by the NCC Chairman, the first Clinical Nutrition Research Unit outside of the United States was established in November 1984. The NCC Chairman has been asked to organize and participate in the program for the symposium to be held in conjunction with the inauguration of the Clinical Nutrition Research Unit. The CNRU will be located in Valencia, Venezuela, and will be funded by the Cavendes Foundation and the University of Carobobo School of Medicine. The establishment of CNRU's in other countries exemplifies the solid foundation upon which the CNRU program is based, the interest of the scientific community in the program, and the overall success that the program has experienced since its inauguration by the NIH.

In addition, the NCC Chairman represents the NIH on the following three DHHS task forces: the DHHS Task Force on Nutrition Objectives, the Interagency Task Force on Implications of the Infant Formula Code for the U.S., and the Task Force on the Assessment of the Scientific Evidence Relating to Problems on Infant Feeding. The report of the Task Force on the Assessment of the Scientific Evidence Relating to Problems on Infant Feeding was published in Pediatrics Vol. 74, #4, part 2, October 1984, supplement.

## HUMAN NUTRITION RESEARCH AND INFORMATION MANAGEMENT SYSTEM

The NCC office staff, supported by the Division of Computer Research and Technology and in collaboration with USDA staff, through the USDA-DHHS Joint Task Force on HNRIM, under the auspices of the Joint Subcommittee on Human Nutrition Research and its successor the Interagency Committee on Human Nutrition Research, developed the Human Nutrition Research and Information Management System, a computerized data base and information retrieval system that includes data on every federally supported nutrition research project.

The development of the HNRIM System began with the work of the NCC. Since 1977, the NCC has retrieved data on NIH projects with nutrition research and training components and their nutrition expenditures, based on the definition of human nutrition research developed by the NCC. The Joint Subcommittee on Human Nutrition Research, operating out of the Office of Science and Technology Policy in the Executive Office of the President, expanded the NIH definition and data collection system to include the human nutrition research activities supported by participating Federal agencies, and developed a system of 34 data classification categories for human nutrition research.

In December 1981, Congress mandated the Secretaries of Agriculture and Health and Human Services to formulate a plan for a Human Nutrition Research and Information Management System. Section 1427 of the National Agricultural Research, Extension and Teaching Policy Act of 1977 (7 U.S.C.-3177), as amended by Section 1425 of the National Agricultural Research, Extension, and Teaching Policy Act Amendments of 1981 (Title XIV of P.L. 97-98) provides as follows:

HUMAN NUTRITION RESEARCH AND INFORMATION MANAGEMENT SYSTEM  
Section 1427. The Secretary [of Agriculture] and the Secretary of Health and Human Services shall formulate and submit to Congress, within one hundred and eighty days after the date of enactment of this section, a plan for a human nutrition research management system. This system shall be based on on-line data support capability allowing for fiscal accounting, management, and control of cross-agency human nutrition research activities. The plan shall provide for management activities of all agencies managing funds for human nutrition research activities under existing authorities and contain recommendations for any additional authorities necessary to achieve a human nutrition research management system.

The Secretaries transmitted the plan to the Congress in July 1982. The plan states that:

The Secretaries of Agriculture and Health and Human Services agree to cooperate in the development of a Human Nutrition Research and Information Management (HNRIM) System. The two departments propose to implement this plan with the advice and assistance of the Joint Subcommittee on Human



Nutrition Research (JSHNR) of the Federal Coordinating Council for Science, Engineering and Technology (FCCSET). Initially the system will use the existing computer facilities of the HHS. However, existing computer facilities and systems supporting human nutrition research management in the Agencies are under review to determine the best long range approach to supporting the objectives of this management information system.

DHHS and USDA formed the joint task force on HNRIM, under the aegis of the JSHNR, which was charged with: 1) reviewing the JSHNR data classification system; 2) defining the elements of the computer system; and 3) implementing the computer system. The task force reviewed and made slight modifications to the JSHNR classification system and developed a detailed data base. In FY 1984, the task force also prepared the second annual progress report on HNRIM for submission to the Congress.

The HNRIM system requires that each participating agency (at present DHHS, USDA, VA, AID, DOD, and DOC-NOAA) assemble and submit its own data; data from all participating agencies are combined into the HNRIM data base. The data base is updated quarterly, but can be updated more frequently if the need arises. The system provides convenient access to information on human nutrition research and research training activities supported in whole or in part by the Federal Government. Fiscal data are limited to actual obligations (expenditures) by the originating Federal agency for the fiscal year in question and do not include state or private support. Federal pass-through funds are reported by the initiating agency. The information contained on projects in the data base includes: project identifier numbers, principal investigator, performing organization name and address, project title, sponsoring organization, congressional district, fiscal year, total funding, percent nutrition, nutrition funding, start data, nutrition classification categories, and a narrative description (abstract). The HNRIM system permits on-line search of any field, including the full text of the narrative. On-line access to over 3,800 nutrition research projects supported by the Federal Government is available through the HNRIM system.

In September and October, 1984, tutorials on the use of the HNRIM system were held at NIH and attended by a total of 36 persons (17 from USDA, 17 from DHHS, and 1 each from AID and the Department of Commerce). Persons who attended the tutorials found them to be useful, informative and helpful. Additional tutorials will be held as needed. At present the HNRIM system is in active use.

#### DHHS RESEARCH INITIATIVE IN NUTRITION (DRIN)

In FY 1979, the NIH was designated as the sponsoring agency to develop the Nutrition Research Initiative, one of the DHHS Health Research Initiatives designed to focus on selected problem areas where mission needs of several DHHS agencies coincide with significant scientific

opportunity. The agencies designated as cosponsors of the initiative were: NIH, ADAMHA, FDA, CDC, NCHS, and HRSA. The NIH-NCC Chairman was designated as the coordinator for developing the initiative.

The purpose of the nutrition initiative is to develop within the DHHS a more comprehensive and effective program of nutrition research and training to strengthen support of related missions. The principal thrust is to reinforce a coherent research program and to extend the growing trans-Institute cooperation in nutrition research to other DHHS agencies. A committee with members from the six agencies that conduct or support nutrition research and training has been given the task to develop a cohesive program for the Department in order to best carry out this initiative in nutrition research. This committee has the following responsibilities:

- o Review and comment on the plans, execution, and results of research efforts, in order to refine and strengthen the Department's nutrition program;
- o Coordinate research stemming from the obesity program, the CNRU's, nutrition research training and manpower development programs, and participation in the Interagency Committee on Human Nutrition Research;
- o Provide information and advice on the nutrition research program to the directors of the agencies involved, to the Office of the Assistant Secretary for Health, and to the Office of the Secretary;
- o Continuously evaluate research data and provide advice for the development of nutrition education materials for the public; and
- o Plan and arrange for conferences, workshops, consensus development exercises, and reports as appropriate.

Several conferences have been held and a number of major activities have been developed under the aegis of DRIN. Some highlights include:

- o The "Conference on the Assessment of Nutritional Status," where the Secretary, DHHS, inaugurated the DRIN with his keynote address. The conference was cosponsored by the NIH-NCC, CDC, and FDA and held at the NIH on September 16-18, 1981. The proceedings of this conference were published in the American Journal of Clinical Nutrition, May 1982 (supplement), volume 35:1089-1325.
- o The "Workshop on Body Weight, Health and Longevity," cosponsored by NIH-NCC and CDC and held January 25-26, 1982. A review of the data and the conclusions of the workshop are described in a paper entitled "Body Weight, Health and Longevity" by Drs. Artemis P. Simopoulos and Theodore Van Itallie, that appeared in the Annals of Internal Medicine, volume 100, no. 2, February 1984.



- o The Joint PA, "NIH New Investigator Research Award (NIRA) in Nutrition: ADAMHA Special Notification for Research on Nutrition and Behavior," which marked the first time that NIH and another agency of the Public Health Service, ADAMHA, supported a Joint PA in nutrition. NIH and ADAMHA published a second Joint PA in March 1984, entitled "Studies on Obesity," which includes the research interests of NIADK, NCI, NHLBI, NIA, NICHD, and NINCDS as well as NIAAA, NIMH and National Institute of Drug Abuse (NIDA).

Since 1979, the participating agencies of DRIN have provided data on their support of nutrition research to the JSHNR. In FY 1982, these agencies along with the other agencies and departments that made up the JSHNR, developed and agreed upon the HNRIM classification system. Subsequently, the participating agencies of DRIN, in collaboration with USDA and the other members of the JSHNR, were instrumental in the formulation of the HNRIM system plan that was transmitted to Congress in July 1982. This effort has since been expanded to provide data on individual grants and projects for incorporation into the previously described HNRIM system.

In FY 1984, the agencies of DRIN developed the Department's 5-Year Plan for Human Nutrition Research and Training, which will be included in the 5-Year Federal Plan for Human Nutrition Research and Training being developed by the Interagency Committee on Human Nutrition Research (ICHNR). NIH was assigned the lead responsibility for the coordination and development of the Public Health Service (PHS) portion of the plan. The NIH priorities for the 5-Year plan were included in the FY 1983 Annual Report of the NIH Program in Biomedical and Behavioral Nutrition Research and Training as appendix F.

#### INTERAGENCY COMMITTEE ON HUMAN NUTRITION RESEARCH

The Interagency Committee on Human Nutrition Research, which succeeded the Joint Subcommittee on Human Nutrition Research in June 1983, is cochaired by the Assistant Secretary for Science and Education, USDA, and the Assistant Secretary for Health, DHHS, and consists of representatives from DHHS; USDA; White House Office of Science and Technology Policy; Department of Commerce, National Oceanic and Atmospheric Administration (DOC/NOAA); Department of Defense (DOD); International Development Cooperative Administration, Agency for International Development (IDCA/AID); National Science Foundation (NSF); the Veterans Administration; and the National Aeronautics and Space Administration (NASA). The NCC Chairman serves as one of the DHHS representatives to the ICHNR.

One of the first efforts of the ICHNR in FY 1984 was the development of the 5-Year Federal Plan for Human Nutrition Research and Training. As noted above, the NIH was assigned the lead responsibility for developing the PHS portion of the plan.



**VII.**  
**APPENDICES**



**APPENDIX A**

**HNRIM CLASSIFICATION SYSTEM  
AND  
FY 1984 NIH EXPENDITURES BY HNRIM CATEGORY AND SPECIAL INTEREST AREA**



HNRIM CLASSIFICATION SYSTEM  
AND  
FY 1984 NIH EXPENDITURES BY HNRIM CATEGORY AND SPECIAL INTEREST AREA

The development of the HNRIM system began with the work of the NCC. Since 1977, the NCC has retrieved data on NIH projects with nutrition research and training components and their nutrition expenditures, based on the definition of human nutrition research developed by the NCC. The Joint Subcommittee on Human Nutrition Research, operating out of the Office of Science and Technology Policy in the Executive Office of the President, expanded the NIH definition and data collection system to include the human nutrition research activities supported by participating Federal agencies, and developed the following system of 34 data classification categories for human nutrition research.

I. Research in the Biomedical and Behavioral Sciences

A. Research on Normal Nutritional Requirements Throughout the Life Cycle

The following five categories are included because of the importance to health promotion of establishing normal nutritional requirements throughout the life cycle, and the differing needs of individuals at various stages of the life cycle.

Research activities relevant to normal nutrition at specific stages of the human life cycle should be assigned to classifications 1-5.

1. Maternal Nutrition
2. Infant and Child Nutrition (0-12 years)  
(includes the low birth weight infant)
3. Adolescent Nutrition (13-18 years)
4. Adult Nutrition (19-65 years)
5. Nutrition of the Elderly (65+ years)

B. Diseases and Conditions

Research on the role of nutrition in the prevention, amelioration, and treatment of diseases and conditions should be assigned to categories 6-16.

6. Cardiovascular Disease and Nutrition
7. Cancer and Nutrition
8. Other Diseases and Nutrition  
(e.g., osteoporosis, diabetes, etc.)



9. Trauma (Including Burns) and Nutrition
10. Infection--Immunology and Nutrition
11. Obesity, Anorexia, and Appetite Control
12. Genetics and Nutrition
13. Nutrition and Function  
(Includes mental, psychomotor, and work performance;  
environmental stress)
14. Nutrient Interactions  
(Includes nutrient-nutrient interactions, nutrient-drug  
interactions, nutrient-toxicant interactions, and nutrient  
toxicity)
15. Other Conditions and Nutrition
16. Nutritional Status  
(Includes research on methods for the determination of  
nutritional status and surveillance: dietary history and  
food consumption, biochemical determinants, anthropometry,  
and clinical examination)

C. Nutrient Metabolism and Metabolic Mechanisms at the Cellular  
and Subcellular Levels

Categories 17-25, 14, and 27 classify research by nutrient variables; these categories should be used to indicate the nutrient variables in research classified elsewhere; and classify biochemical, subcellular, cellular, and animal research, such as studies of nutrient mechanisms and metabolism not related to specific diseases, conditions, or stages of the life cycle.

17. Carbohydrates
18. Lipids (Fats and Oils)  
(Includes essential fatty acids, lipo- and apoproteins)
19. Alcohols  
(Includes ethanol, sorbitols, and other alcohols used as  
components in synthetic and semisynthetic foods)
20. Proteins and Amino Acids  
(Includes essential as well as nonessential amino acids  
such as taurine and carnitine)
21. Vitamins  
(Includes vitamin A, C, B<sub>6</sub>, B<sub>12</sub>, D, E, K, thiamin,  
riboflavin, niacin, folacin, biotin, and pantothenic  
acid)

- 22. Minerals and Essential Trace Elements  
(Includes calcium, phosphorus, magnesium, iron, zinc, iodine, copper, manganese, fluoride, chromium, selenium, and molybdenum)
- 23. Water and Electrolytes  
(Includes sodium, potassium, and chloride)
- 24. Fiber
- 25. Other Nutrients in Food  
(Such as cobalt, nickel, vanadium, silicon, tin, arsenic, cadmium, choline, lecithin and various growth factors)
- \*14. Nutrient Interactions  
(Includes nutrient-nutrient interactions, nutrient-drug interactions, nutrient-toxicant interactions, and nutrient toxicity)
- \*27. Bioavailability of Nutrients  
(Includes methods for the determination of bioavailability of nutrients)

## II. Research in Food Sciences

Categories 26-29 should be used for research in the nutritional aspects of food sciences.

- 26. Food Composition  
(Includes nutritional quality, nutrient content, and research on methods of analysis for nutrients and fiber)
- 27. Bioavailability of Nutrients  
(Includes methods for the determination of bioavailability of nutrients)
- 28. Effects of Technology on Acceptability and Nutritional Characteristics of Foods and Diets  
(Includes the beneficial and adverse effects of varietal and species differences, harvest and post-harvest technology, retail food practices, food processing, handling, preservation, and home cooking.)
- 29. Other Research in Food Sciences

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\* This category is listed here to indicate that it may also be applicable to research on Nutrient Metabolism and Metabolic Mechanisms at the Cellular and Subcellular Levels (Class I.C).

### III. Research on Nutrition Monitoring and Surveillance of Populations

#### 30. Food Consumption Surveys

(Includes research on methods for determination of food consumption and its trends, and research utilizing data derived from such surveys.)

#### 31. Studies of Dietary Practices, Food Consumption Patterns, and Their Determinants.

#### \*\*16. Nutritional Status

(Includes research on methods for the determination of nutritional status and surveillance: dietary history and food consumption, biochemical determinants, anthropometry, and clinical examination)

### IV. Research in Nutrition Education

Categories 32-33 encompass research in nutrition education.

#### 32. Studies on Methods for Informing and Educating the Public About Nutrition, Health, and Dietary Practices and for Countering Nutrition Misinformation

(Includes studies on methods for informing and educating professionals in these areas.)

#### 33. Other Research in Nutrition Education

### V. Research on the Effects of Government Policy and Socioeconomic Factors on Food Consumption and Human Nutrition

#### 34. Effects of Government Policy and Socioeconomic Factors on Food Consumption and Human Nutrition.

The following table indicates the NIH nutrition research support in the 34 HNRIM classification categories along with the number of grants and contracts. The column labeled 'percent of total' represents the funds expended in a given category in relation to total expenditures for nutrition research and research training, which for FY 1984 amounted to \$192,918,000. It should be pointed out that a grant or contract may appear in more than one category. For example, a project on maternal PKU may appear under maternal nutrition and under genetics. Thus, the total expenditures in the 34 categories are larger than the sum of \$192,918,000. It should be noted that while NIH nutrition research encompasses all 34 classification categories, by far the largest component of NIH nutrition research is concentrated in area I, Research in the Bio-medical and Behavioral Sciences.

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\*\* This category is listed here because it may also be applicable to Nutrition Monitoring and Surveillance of Populations.

TABLE A-1

FY 1984 NIH EXPENDITURES  
IN THE 34 HNRIM CLASSIFICATION CATEGORIES

Nutrition Research Classification		Number of Grants and Contracts	Expenditure* (in thousands of dollars)	Percent of Total**
Code	Area			
I. <u>Research in the Biomedical and Behavioral Sciences</u>				
1.	Maternal Nutrition	127	10,587	5
2.	Infant and Child Nutr.	344	35,239	18
3.	Adolescent Nutrition	41	5,069	3
4.	Adult Nutrition	46	5,804	3
5.	Nutr. of the Elderly	125	7,824	4
6.	Cardiovascular Disease and Nutrition	355	50,993	26
7.	Cancer and Nutrition	658	53,824	28
8.	Other Diseases and Nutr.	290	27,132	15
9.	Trauma (Burns) and Nutr.	37	2,998	2
10.	Infection, Immunology, and Nutrition	167	10,060	5
11.	Obesity, Anorexia, and Appetite Control	251	24,227	13
12.	Genetics and Nutrition	272	31,486	16
13.	Nutrition and Function	310	32,558	17
14.	Nutrient-Nutrient/Drug/ Toxicant Interactions	313	27,212	14
15.	Other Conditions & Nutr.	269	24,535	13
16.	Res. on Nutr. Status	351	35,116	18

(TABLE A-1 continued)

<u>Nutrition Research Classification</u>		<u>Number of Grants and Contracts</u>	<u>Expenditure*</u>	<u>Percent of Total**</u>
<u>Code</u>	<u>Area</u>			
17.	Carbohydrates	119	10,228	5
18.	Lipids (Fats and Oils)	396	58,441	30
19.	Alcohols	38	3,878	2
20.	Proteins and Amino Acids	255	22,947	12
21.	Vitamins	538	53,821	28
22.	Minerals & Trace Elements	264	30,875	16
23.	Water and Electrolytes	122	20,700	11
24.	Fiber	31	7,567	4
25.	Other Nutrients in Food	32	2,963	2
26.	Food Composition	55	5,827	3
27.	Bioavailability	52	5,040	3
<u>II. Research in Food Sciences</u>				
28.	Effects of Technology on Foods and Diets	25	2,223	1
		14	1,222	1
29.	Other Res. In Food Sci.			
<u>III. Research on Nutrition Monitoring &amp; Surveillance of Populations</u>				
30.	Food Consumption Surveys, R&D	22	2,472	1
31.	Research on Dietary Practices, Food Consumpt., etc.	80	8,812	5
<u>IV. Research in Nutrition Education</u>				
32.	Methods for Educating & Informing the Public	94	14,235	7
33.	Other Research in Nutr. Ed.	16	375	0



(Table A-1 continued)

Nutrition Research		Number of Grants and Contracts	Expenditure*	Percent of Total**
Classification				
Code	Area			
<u>V. Research on the Effects of Government Policy and Socioeconomic Factors on Food Consumption and Human Nutrition</u>				
34.	Effects of Govt. Policy & Socioeconomic Factors	2	7	0
*A grant or contract may be assigned to more than one of these areas.				
**The total expenditure of the NIH nutrition program in FY 1984 was \$192,918,000.				

In addition to the 34 HNRIM categories, there are 6 areas of particular scientific or political interest to NIH. These six "Special Interest Areas" are: nutrition and prevention of disease, total parenteral and enteral nutrition, epidemiological research in nutrition, international nutrition research, nutrition education for the public, and nutrition education for professionals. The number of grants and contracts, the FY 1984 expenditures for these grants and contracts, and the percentage that these expenditures are of the total NIH nutrition program are displayed in the following table.

TABLE A-2

NIH EXPENDITURES IN SPECIAL INTEREST AREAS  
IN NUTRITION RESEARCH AND EDUCATION

Special Interest Area	No. of Grants or Contracts*	Expenditure* (in thousands of dollars)	Percent of Total**
SI-1. Prevention of Disease	1,183	120,251	62
SI-2. Total Parenteral and Enteral Nutrition	82	7,458	4
SI-3. Epidemiological Research	216	35,447	18
SI-4. International Research	48	9,470	5
SI-5. Education for the Public	24	6,227	3
SI-6. Educ. for Professionals	73	1,303	1
*A grant or contract may be assigned to more than one of these areas.			
**The total expenditure of the NIH nutrition program in FY 1984 was \$192,918,000.			



**APPENDIX B**

**FY 1984 NUTRITION EXPENDITURES OF THE 11 INSTITUTES,  
DIVISION OF RESEARCH RESOURCES, AND  
FOGARTY INTERNATIONAL CENTER**



TABLE B-1

National Cancer Institute  
BIOMEDICAL AND BEHAVIORAL NUTRITION RESEARCH AND TRAINING, FY 1984  
BY CATEGORY OF SUPPORT  
(Actual Obligations, in thousands of dollars)

		<u>Breakdown</u>		<u>Total</u>	
	<u>Item</u>	<u>Number</u>	<u>Cost</u>	<u>Number</u>	<u>Cost</u>
<u>Extramural</u>					
Research grants:	Regular . . . . .	340	22,151		
	Clinical trials . . . . .	117	5,346		
	Total . . . . .			457	27,497
Program projects:	Regular . . . . .	20	4,986		
	Clinical trials . . . . .	4	1,204		
	Total . . . . .			24	6,190
Contracts:	Regular . . . . .	40	9,268		
	Clinical trials . . . . .	1	479		
	Total . . . . .			41	9,747
Centers:	Regular . . . . .	28	1,966		
	Clinical trials . . . . .	0	0		
	Total . . . . .			28	1,966
Research Resources Support.				0	0
Reimbursement Agreements.				10	1,170
Research Career Development Awards.				8*	163
New Investigator Research Awards.				12*	413
Training:	Training grants . . . . .	68*	455		
	Fellowships . . . . .	0*	0		
	Total . . . . .			68*	<u>455</u>
Subtotal - Extramural . . . . .					\$ 47,601
<u>Intramural</u>					
Projects.				28	2,518
Training.				0*	<u>0</u>
Subtotal - Intramural . . . . .					\$ 2,518
TOTAL NUTRITION RESEARCH AND TRAINING - NCI . . . . .					\$ 50,119

\*Number of persons.

NOTE: The cost figures in this table reflect only research falling within the definition of nutrition research.



TABLE B-2

National Heart, Lung, and Blood Institute  
BIOMEDICAL AND BEHAVIORAL NUTRITION RESEARCH AND TRAINING, FY 1984,  
BY CATEGORY OF SUPPORT  
(Actual Obligations, in thousands of dollars)

		<u>Breakdown</u>		<u>Total</u>	
	<u>Item</u>	<u>Number</u>	<u>Cost</u>	<u>Number</u>	<u>Cost</u>
<u>Extramural</u>					
Research grants:	Regular . . . . .	154	18,450		
	Clinical trials . . . . .	14	5,929		
	Total . . . . .			168	24,379
Program projects:	Regular . . . . .	14	6,465		
	Clinical trials . . . . .	0	0		
	Total . . . . .			14	6,465
Contracts:	Regular . . . . .	10	1,418		
	Clinical trials . . . . .	15	940		
	Total . . . . .			25	2,358
Centers:	Regular . . . . .	10	7,329		
	Clinical trials . . . . .	1	64		
	Total . . . . .			11	7,393
Research Resources Support. . . . .				0	0
Reimbursement Agreements. . . . .				7	495
Research Career Development Awards. . . . .				24*	412
New Investigator Research Awards. . . . .				10*	176
Training:	Training grants . . . . .	138*	994		
	Fellowships . . . . .	6*	68		
	Total . . . . .			144*	<u>1,062</u>
Subtotal - Extramural . . . . .				\$	42,740
<u>Intramural</u>					
Projects. . . . .				10	1,720
Training. . . . .				12*	<u>93</u>
Subtotal - Intramural . . . . .				\$	1,813
TOTAL NUTRITION RESEARCH AND TRAINING - NHLBI . . . . .				\$	44,553

\*Number of persons.

NOTE: The cost figures in this table reflect only research falling within the definition of nutrition research.

TABLE B-3

National Institute of Dental Research  
BIOMEDICAL AND BEHAVIORAL NUTRITION RESEARCH AND TRAINING, FY 1984,  
BY CATEGORY OF SUPPORT  
(Actual Obligations, in thousands of dollars)

	Item	Breakdown		Total	
		Number	Cost	Number	Cost
<u>Extramural</u>					
Research grants:	Regular . . . . .	10	334		
	Clinical trials . . . . .	0	0		
	Total . . . . .			10	334
Program projects:	Regular . . . . .	1	103		
	Clinical trials . . . . .	0	0		
	Total . . . . .			1	103
Contracts:	Regular . . . . .	5	468		
	Clinical trials . . . . .	0	0		
	Total . . . . .			5	468
Centers:	Regular . . . . .	1	209		
	Clinical trials . . . . .	0	0		
	Total . . . . .			1	209
Research Resources Support.				0	0
Reimbursement Agreements.				0	0
Research Career Development Awards.				1*	0
New Investigator Research Awards.				0*	0
Training:	Training grants . . . . .	10*	233		
	Fellowships . . . . .	2*	20		
	Total . . . . .			12*	<u>253</u>
Subtotal - Extramural . . . . .				\$	1,367
<u>Intramural</u>					
Projects.				5	52
Training.				0*	0
Subtotal - Intramural . . . . .				\$	<u>52</u>
TOTAL NUTRITION RESEARCH AND TRAINING - NIDR. . . . .				\$	1,419

\*Number of persons.

NOTE: The cost figures in this table reflect only research falling within the definition of nutrition research.

TABLE B-4

National Institute of Arthritis, Diabetes, and  
Digestive and Kidney Diseases  
BIOMEDICAL AND BEHAVIORAL NUTRITION RESEARCH AND TRAINING, FY 1984,  
BY CATEGORY OF SUPPORT  
(Actual Obligations, in thousands of dollars)

		<u>Breakdown</u>		<u>Total</u>	
	<u>Item</u>	<u>Number</u>	<u>Cost</u>	<u>Number</u>	<u>Cost</u>
<u>Extramural</u>					
Research grants:	Regular . . . . .	400	25,680		
	Clinical trials . . . . .	8	292		
	Total . . . . .			408	25,972
Program projects:	Regular . . . . .	9	1,982		
	Clinical trials . . . . .	0	0		
	Total . . . . .			9	1,982
Contracts:	Regular . . . . .	1	61		
	Clinical trials . . . . .	0	0		
	Total . . . . .			1	61
Centers:	Regular . . . . .	7	2,659		
	Clinical trials . . . . .	0	0		
	Total . . . . .			7	2,659
Research Resources Support. . . . .				0	0
Reimbursement Agreements. . . . .				0	0
Research Career Development Awards. . . . .				22*	576
New Investigator Research Awards. . . . .				25*	612
Training:	Training grants . . . . .	41*	617		
	Fellowships . . . . .	6*	96		
	Total . . . . .			47*	<u>713</u>
Subtotal - Extramural . . . . .				\$	32,575
<u>Intramural</u>					
Projects. . . . .				38	3,059
Training. . . . .				13*	<u>335</u>
Subtotal - Intramural . . . . .				\$	3,394
TOTAL NUTRITION RESEARCH AND TRAINING - NIADDK. . .				\$	35,969

\*Number of persons.

NOTE: The cost figures in this table reflect only research falling within the definition of nutrition research.

TABLE B-5

National Institute of Neurological and Communicative  
Disorders and Stroke  
BIOMEDICAL AND BEHAVIORAL NUTRITION RESEARCH AND TRAINING, FY 1984,  
BY CATEGORY OF SUPPORT  
(Actual Obligations, in thousands of dollars)

Item	Breakdown		Total	
	Number	Cost	Number	Cost
<u>Extramural</u>				
Research grants:				
Regular . . . . .	28	2,210		
Clinical trials . . . . .	0	0		
Total . . . . .			28	2,210
Program projects:				
Regular . . . . .	2	244		
Clinical trials . . . . .	1	30		
Total . . . . .			3	274
Contracts:				
Regular . . . . .	0	0		
Clinical trials . . . . .	0	0		
Total . . . . .			0	0
Centers:				
Regular . . . . .	1	48		
Clinical trials . . . . .	0	0		
Total . . . . .			1	48
Research Resources Support. . . . .			0	0
Reimbursement Agreements. . . . .			0	0
Research Career Development Awards. . . . .			0*	0
New Investigator Research Awards. . . . .			3*	120
Training:				
Training grants . . . . .	0*	0		
Fellowships . . . . .	0*	0		
Total . . . . .			0*	0
Subtotal - Extramural . . . . .			\$	2,652
<u>Intramural</u>				
Projects. . . . .			0	0
Training. . . . .			0*	0
Subtotal - Intramural . . . . .			\$	0
TOTAL NUTRITION RESEARCH AND TRAINING - NINCDS. . . . .			\$	2,652

\*Number of persons.

NOTE: The cost figures in this table reflect only research falling within the definition of nutrition research.

TABLE B-6

National Institute of Allergy and Infectious Diseases  
BIOMEDICAL AND BEHAVIORAL NUTRITION RESEARCH AND TRAINING, FY 1984,  
BY CATEGORY OF SUPPORT  
(Actual Obligations, in thousands of dollars)

Item	Breakdown		Total	
	Number	Cost	Number	Cost
<u>Extramural</u>				
Research grants:				
Regular . . . . .	21	1,327		
Clinical trials . . . . .	0	0		
Total . . . . .			21	1,327
Program projects:				
Regular . . . . .	1	167		
Clinical trials . . . . .	0	0		
Total . . . . .			1	167
Contracts:				
Regular . . . . .	1	25		
Clinical trials . . . . .	0	0		
Total . . . . .			1	25
Centers:				
Regular . . . . .	0	0		
Clinical trials . . . . .	0	0		
Total . . . . .			0	0
Research Resources Support. . . . .			0	0
Reimbursement Agreements. . . . .			1	0
Research Career Development Awards. . . . .			1*	18
New Investigator Research Awards. . . . .			1*	0
Training:				
Training grants . . . . .	4*	7		
Fellowships . . . . .	2*	18		
Total . . . . .			6*	25
Subtotal - Extramural . . . . .			\$	1,562
<u>Intramural</u>				
Projects. . . . .			1	84
Training. . . . .			0*	0
Subtotal - Intramural . . . . .			\$	84
TOTAL NUTRITION RESEARCH AND TRAINING - NIAID . . . . .			\$	1,646

\*Number of persons.

NOTE: The cost figures in this table reflect only research falling within the definition of nutrition research.



TABLE B-7

National Institute of General Medical Sciences  
BIOMEDICAL AND BEHAVIORAL NUTRITION RESEARCH AND TRAINING, FY 1984,  
BY CATEGORY OF SUPPORT  
(Actual Obligations, in thousands of dollars)

		<u>Breakdown</u>		<u>Total</u>	
	<u>Item</u>	<u>Number</u>	<u>Cost</u>	<u>Number</u>	<u>Cost</u>
<u>Extramural</u>					
Research grants:	Regular . . . . .	11	966		
	Clinical trials . . . . .	0	0		
	Total . . . . .			11	966
Program projects:	Regular . . . . .	1	91		
	Clinical trials . . . . .	0	0		
	Total . . . . .			1	91
Contracts:	Regular . . . . .	0	0		
	Clinical trials . . . . .	0	0		
	Total . . . . .			0	0
Centers:	Regular . . . . .	3	926		
	Clinical trials . . . . .	0	0		
	Total . . . . .			3	926
Research Resources Support.				0	0
Reimbursement Agreements.				0	0
Research Career Development Awards.				0*	0
New Investigator Research Awards.				3*	80
Training:	Training grants . . . . .	10*	208		
	Fellowships . . . . .	1*	0		
	Total . . . . .			11*	<u>208</u>
Subtotal - Extramural . . . . .				\$	2,271
<u>Intramural</u>					
Projects.				0	0
Training.				0*	<u>0</u>
Subtotal - Intramural . . . . .				\$	0
TOTAL NUTRITION RESEARCH AND TRAINING - NIGMS . . .				\$	2,271

\*Number of persons.

NOTE: The cost figures in this table reflect only research falling within the definition of nutrition research.

TABLE B-8

National Institute of Child Health and Human Development  
 BIOMEDICAL AND BEHAVIORAL NUTRITION RESEARCH AND TRAINING, FY 1984,  
 BY CATEGORY OF SUPPORT  
 (Actual Obligations, in thousands of dollars)

	Item	Breakdown		Total	
		Number	Cost	Number	Cost
<u>Extramural</u>					
Research grants:	Regular . . . . .	176	11,078		
	Clinical trials . . . . .	11	1,034		
	Total . . . . .			187	12,112
Program projects:	Regular . . . . .	11	2,089		
	Clinical trials . . . . .	3	1,726		
	Total . . . . .			14	3,815
Contracts:	Regular . . . . .	23	1,921		
	Clinical trials . . . . .	1	297		
	Total . . . . .			24	2,218
Centers:	Regular . . . . .	12	690		
	Clinical trials . . . . .	0	0		
	Total . . . . .			12	690
Research Resources Support. . . . .				3	21
Reimbursement Agreements. . . . .				2	260
Research Career Development Awards. . . . .				11*	334
New Investigator Research Awards. . . . .				17*	573
Training:	Training grants . . . . .	22*	280		
	Fellowships . . . . .	12*	62		
	Total . . . . .			34*	342
Subtotal - Extramural . . . . .				\$	20,365
<u>Intramural</u>					
Projects. . . . .				24	3,787
Training. . . . .				28*	0
Subtotal - Intramural . . . . .				\$	3,787
TOTAL NUTRITION RESEARCH AND TRAINING - NICHD . . .				\$	24,152

\*Number of persons.

NOTE: The cost figures in this table reflect only research falling within the definition of nutrition research.

TABLE B-9

National Eye Institute  
BIOMEDICAL AND BEHAVIORAL NUTRITION RESEARCH AND TRAINING, FY 1984,  
BY CATEGORY OF SUPPORT  
(Actual Obligations, in thousands of dollars)

	Item	Breakdown		Total	
		Number	Cost	Number	Cost
<u>Extramural</u>					
Research grants:	Regular . . . . .	47	3,382		
	Clinical trials . . . . .	0	0		
	Total . . . . .			47	3,382
Program projects:	Regular . . . . .	0	0		
	Clinical trials . . . . .	0	0		
	Total . . . . .			0	0
Contracts:	Regular . . . . .	0	0		
	Clinical trials . . . . .	0	0		
	Total . . . . .			0	0
Centers:	Regular . . . . .	0	0		
	Clinical trials . . . . .	0	0		
	Total . . . . .			0	0
Research Resources Support. . . . .				0	0
Reimbursement Agreements. . . . .				0	0
Research Career Development Awards. . . . .				1*	2
New Investigator Research Awards. . . . .				3*	170
Training:	Training grants . . . . .	0*	0		
	Fellowships . . . . .	2*	41		
	Total . . . . .			2*	<u>41</u>
Subtotal - Extramural . . . . .				\$	3,595
<u>Intramural</u>					
Projects. . . . .				8	1,016
Training. . . . .				0*	<u>0</u>
Subtotal - Intramural . . . . .				\$	1,016
TOTAL NUTRITION RESEARCH AND TRAINING - NEI . . . .				\$	4,611

\*Number of persons.

NOTE: The cost figures in this table reflect only research falling within the definition of nutrition research.

TABLE B-10

National Institute of Environmental Health Sciences  
BIOMEDICAL AND BEHAVIORAL NUTRITION RESEARCH AND TRAINING, FY 1984,  
BY CATEGORY OF SUPPORT  
(Actual Obligations, in thousands of dollars)

		Breakdown		Total	
	Item	Number	Cost	Number	Cost
<u>Extramural</u>					
Research grants:	Regular . . . . .	14	1,198		
	Clinical trials . . . . .	0	0		
	Total . . . . .			14	1,198
Program projects:	Regular . . . . .	1	570		
	Clinical trials . . . . .	0	0		
	Total . . . . .			1	570
Contracts:	Regular . . . . .	0	0		
	Clinical trials . . . . .	0	0		
	Total . . . . .			0	0
Centers:	Regular . . . . .	0	0		
	Clinical trials . . . . .	0	0		
	Total . . . . .			0	0
Research Resources Support. . . . .				0	0
Reimbursement Agreements. . . . .				0	0
Research Career Development Awards. . . . .				0*	0
New Investigator Research Awards. . . . .				0*	0
Training:	Training grants . . . . .	0*	0		
	Fellowships . . . . .	0*	0		
	Total . . . . .			0*	0
Subtotal - Extramural . . . . .				\$	1,768
<u>Intramural</u>					
Projects. . . . .				0	0
Training. . . . .				0*	0
Subtotal - Intramural . . . . .				\$	0
TOTAL NUTRITION RESEARCH AND TRAINING - NIEHS . . .				\$	1,768

\*Number of persons.

NOTE: The cost figures in this table reflect only research falling within the definition of nutrition research.

TABLE B-11

National Institute on Aging  
BIOMEDICAL AND BEHAVIORAL NUTRITION RESEARCH AND TRAINING, FY 1984,  
BY CATEGORY OF SUPPORT  
(Actual Obligations, in thousands of dollars)

Item	Breakdown		Total	
	Number	Cost	Number	Cost
<u>Extramural</u>				
Research grants:	Regular . . . . .	53	2,497	
	Clinical trials . . . . .	0	0	
	Total . . . . .		53	2,497
Program projects:	Regular . . . . .	8	1,577	
	Clinical trials . . . . .	0	0	
	Total . . . . .		8	1,577
Contracts:	Regular . . . . .	0	0	
	Clinical trials . . . . .	0	0	
	Total . . . . .		0	0
Centers:	Regular . . . . .	0	0	
	Clinical trials . . . . .	0	0	
	Total . . . . .		0	0
Research Resources Support. . . . .			0	0
Reimbursement Agreements. . . . .			1	63
Research Career Development Awards. . . . .			17*	100
New Investigator Research Awards. . . . .			4*	75
Training:	Training grants . . . . .	32*	4	
	Fellowships . . . . .	1*	9	
	Total . . . . .		33*	<u>13</u>
Subtotal - Extramural . . . . .			\$	4,325
<u>Intramural</u>				
Projects. . . . .			5	432
Training. . . . .			0*	<u>0</u>
Subtotal - Intramural . . . . .			\$	432
TOTAL NUTRITION RESEARCH AND TRAINING - NIA . . . .			\$	4,757

\*Number of persons.

NOTE: The cost figures in this table reflect only research falling within the definition of nutrition research.

TABLE B-12

Division of Research Resources  
BIOMEDICAL AND BEHAVIORAL NUTRITION RESEARCH AND TRAINING, FY 1984,  
BY CATEGORY OF SUPPORT  
(Actual Obligations, in thousands of dollars)

	Item	Breakdown		Total	
		Number	Cost	Number	Cost
<u>Extramural</u>					
Research grants:	Regular . . . . .	0	0		
	Clinical trials . . . . .	0	0		
	Total . . . . .			0	0
Program projects:	Regular . . . . .	0	0		
	Clinical trials . . . . .	0	0		
	Total . . . . .			0	0
Contracts:	Regular . . . . .	0	0		
	Clinical trials . . . . .	0	0		
	Total . . . . .			0	0
Centers:	Regular . . . . .	0	0		
	Clinical trials . . . . .	0	0		
	Total . . . . .			0	0
Research Resources Support. . . . .				285	18,870
Reimbursement Agreements. . . . .				0	0
Research Career Development Awards. . . . .				0*	0
New Investigator Research Awards. . . . .				0*	0
Training:	Training grants . . . . .	2*	4		
	Fellowships . . . . .	0*	0		
	Total . . . . .			2*	<u>4</u>
Subtotal - Extramural . . . . .				\$	18,874
<u>Intramural</u>					
Projects. . . . .				0	0
Training. . . . .				0*	<u>0</u>
Subtotal - Intramural . . . . .				\$	0
TOTAL NUTRITION RESEARCH AND TRAINING - DRR . . . .				\$	18,874

\*Number of persons.

NOTE: The cost figures in this table reflect only research falling within the definition of nutrition research.



TABLE B-13

Fogarty International Center  
BIOMEDICAL AND BEHAVIORAL NUTRITION RESEARCH AND TRAINING, FY 1984,  
BY CATEGORY OF SUPPORT  
(Actual Obligations, in thousands of dollars)

Item	Breakdown		Total	
	Number	Cost	Number	Cost
<u>Extramural</u>				
Research grants:				
Regular . . . . .	1	1		
Clinical trials . . . . .	0	0		
Total . . . . .			1	1
Program projects:				
Regular . . . . .	0	0		
Clinical trials . . . . .	0	0		
Total . . . . .			0	0
Contracts:				
Regular . . . . .	0	0		
Clinical trials . . . . .	0	0		
Total . . . . .			0	0
Centers:				
Regular . . . . .	0	0		
Clinical trials . . . . .	0	0		
Total . . . . .			0	0
Research Resources Support. . . . .			0	0
Reimbursement Agreements. . . . .			0	0
Research Career Development Awards. . . . .			0*	0
New Investigator Research Awards. . . . .			0*	0
Training:				
Training grants . . . . .	0*	0		
Fellowships . . . . .	3*	126		
Total . . . . .			3*	126
Subtotal - Extramural . . . . .			\$	127
<u>Intramural</u>				
Projects. . . . .			0	0
Training. . . . .			0*	0
Subtotal - Intramural . . . . .			\$	0
TOTAL NUTRITION RESEARCH AND TRAINING - FIC . . . . .			\$	127

\*Number of persons.

NOTE: The cost figures in this table reflect only research falling within the definition of nutrition research.



## **APPENDIX C**

### **DESCRIPTION OF THE EXTRAMURAL AND THE INTRAMURAL NUTRITION RESEARCH AND RESEARCH TRAINING PROGRAMS**



## DESCRIPTION OF THE EXTRAMURAL AND THE INTRAMURAL NUTRITION RESEARCH AND RESEARCH TRAINING PROGRAMS

### THE EXTRAMURAL RESEARCH PROGRAM

The major component of the NIH nutrition program is the extramural research program carried out at various universities; in graduate science departments, principally departments of nutrition; and in medical, dental, and other health professional schools, especially schools of public health. The extramural program is described under two major categories: the research program, and manpower development.

#### The Research Program

Nutrition research supported by NIH includes the effects of nutrients on human growth and development, health maintenance and promotion, disease prevention, and disease treatment. The primary nutrition mission of NIH lies in biomedical and behavioral research and training. In addition, NIH funds nutrition education for professionals and the public as an integral part of many research programs and provides the public with nutrition pamphlets, public service announcements on radio and television, and materials for magazine articles. Nutrition education for professionals is provided through various scientific publications, conferences, and workshops. Appendix K describes the Institutes' legislative authorities for nutrition research.

All 11 Institutes and DRR support research on requirements and basic metabolism of nutrients, the assessment of nutritional status of patients and populations, and the role of nutrition in health promotion and disease prevention. The following is a brief overview of the extramural activities of these Institutes.

Studies supported by the National Cancer Institute reflect a continuing interest in determining the role of nutrition in cancer. These projects, designed to test a diverse set of hypotheses, range from basic research that attempts to determine the role of specific nutrients in tumorigenesis to epidemiologic investigations that attempt to correlate risk factors and dietary intakes. Research in cancer etiology, biology, diagnosis, prevention, and treatment is being carried out in universities, research centers, and hospitals both in the United States and abroad. Funding mechanisms that support these activities include contracts, grants, and cooperative agreements.

Among the topics of interest is the relationship of specific lifestyles and dietary habits of various populations to cancer incidence. Studies have been designed to explore the question of whether dietary components serve as risk factors apart from other environmental factors in the etiology of various site specific cancers.

In response to a pressing need for food composition data, the NCI's Division of Cancer Prevention and Control (DCPC) is supporting three projects designed to develop analytical methods for determining new

mineral and fiber content data. In addition, an interagency agreement with USDA is in effect to define further the quality and form of specific dietary factors in the food supply. Being investigated is the bioavailability, biochemical effects, and interactions with other nutrients. The first of these investigations deals with organic and inorganic forms of selenium (Se) and pharmacokinetics and bioavailability of this mineral.

The need for the development of more efficient and reliable methods and tools for the assessment of dietary intake are also being addressed. Three investigators are working on refining and developing self-administered food frequency questionnaires. The first of these studies entails reassessing dietary intake among female, registered nurse, cohort members in 1986 using an expanded, more detailed, and optically scannable version of the previously administered semiquantitative food frequency questionnaire. The additional data will reduce misclassification of dietary exposure and provide a means to test a wide variety of hypotheses relating dietary factors to cancer incidence.

Measures of dietary selenium, retinol, carotenes, alpha-tocopherol, and vitamins A and C obtained through use of the questionnaire also will be assessed by analyzing the associations between serum and computer estimates of the intakes of these nutrients. These studies will provide valuable methodologic information on the validity of retrospective food frequency techniques and the implications of using a single plasma nutrient level determination.

Microcomputer applications of dietary data collection methodologies in free-living populations and nutritional assessment software designed to relate measured clinical and metabolic responses are also being investigated.

Studies are examining the relationship of various dietary components on the mechanisms of carcinogenesis, i.e., promotional phases of neoplastic cell evolution and growth, and carcinogenic sequestration.

Basic research is under way to examine the role of calcium and macromolecular growth factors in cell proliferation. Another study is focusing on the effectiveness of retinoids as chemopreventive agents. This study is exploring the inhibitory effect of the combined treatments with 13-cis-retinoic and alpha-difluoro-methylornithine (DEMO) on 12-o-tetradecanoylphorbol-13-acetate (TPA) promoted skin tumors. The possible toxic effects of the use of these retinoids will also be explored.

Investigators are also examining the dietary bioavailability of selenium through the use of stable isotope enrichment and double labeling techniques. Data gained from these studies will provide needed information on fundamental features of selenium nutrition. Others are exploring the roles of estradiol and testosterone in the development of breast malignancies and defining the role of 1,25 dihydroxyvitamin D<sub>3</sub> in the maintenance and proliferation of malignant cells.



A number of investigations are being funded to examine the anticarcinogenic actions of natural and synthetic inhibitors. Among the natural products under study are orange peel; cabbage and peas, onion, garlic and soybean isolates; Bowman-birk soybean inhibitor; dietary lipotropes; and new natural inhibitors such as ellagic acid and leguminosae.

In concert with these studies, funding has been made available to determine safe dosages of various chemopreventive agents. Phase I studies of available patients will define the safely delivery dose of each investigational new chemopreventive agent, characterize minimum toxicity by organ site, reversibility and dose relationship, and recommend a phase II-III starting dose and schedule. A pilot data base on cancer chemoprevention testing in experimental animals has also been funded.

The relationship of an individual's intake of alcohol, caffeine, and fat to the development of cancer is also being investigated. Studies on stomach and laryngeal-hypopharyngeal cancers are aimed at determining the distribution and chemical identity of mutagenic compounds in red, rose, white, and dessert wines and the evaluation of the relative carcinogenicity of a variety of such beverages.

The potential impact of coffee constituents upon the glutathione S-8 transferase (GSA) system is the subject of one study. Determining whether dietary excesses of caffeine containing products fed to experimental animals influence tumorigenesis is a major consideration of another study. The interaction of caffeine and high fat diets on DMBA induced rat mammary carcinoma model will also be studied.

Studies have also been designed to further examine the role of fat in the development of cancer. For example, investigations are seeking to elucidate the functions of types and levels of dietary lipid and to gain new insights on the interaction of selenium, vitamin E, saturated fat and polyunsaturated fat and colon carcinogenesis. Animals in these studies will be fed diets containing these variables. The effects of these diets on the activities of glutathione peroxidase and glutathione S-transferase will be determined. Interactions of other variables will also be observed.

Lard is being utilized in a study designed to determine events related to mammary tumor initiation in rodents fed diets high in fat. In vitro fat studies will also examine novel mechanisms in intercellular communications and exposure of cells to ionizing radiation.

An epidemiological study proposes to assess the interrelationships of major nutrients with various steroid and polypeptide hormones and breast cancer. Seventh-Day Adventist vegetarian and SDA nonvegetarian premenopausal women will be studied.

Two multi-institutional trials are being funded to assess the influence of a low fat diet (20 percent of calories as fat) on the devel-

opment of breast cancer in women at increased risk and as an adjuvant in women with stage II breast cancer. To be determined are (a) the acceptance of low fat diets, (b) methods to enhance compliance, (c) extent to which control subjects modify diet, (d) degree of fluctuation in fat intake in both groups, and (e) interactions between cytotoxic drugs and low fat diets.

Also in the area of clinical trials, a 5-year randomized double-blind retinoid project is designed to evaluate the effectiveness of low dosage levels of isotretinoin in reducing the incidence of basal cell carcinomas. Clinical trials are also designed to test the efficacy of nutritional supplements, including beta-carotene, vitamin C and vitamin E, in preventing adenomatous polyps of the large bowel in persons at high risk.

Anorexia still remains as a major complicating factor in the treatment of the patient with cancer. An attempt to develop a deeper understanding of the abnormalities in anorectic tumor-bearing subjects is the objective of a study designed to assess the effects of insulin treatment on systems thought to mediate hunger and satiety. The role of amine neurotransmitters in mediating cancer anorexia is also under investigation. Studies utilizing "scapegoat" foods are being conducted to improve understanding of the nature of chemotherapy induced food aversions and the potential for blocking their development.

Another study is under way to determine the benefits of gallium nitrate in the treatment of cancer related hypercalcemia. Gallium nitrate has been shown to directly inhibit in vitro bone resorption. This project will establish a minimal effective dose and compare gallium nitrate with the best currently available standard treatment for patients with resistance cancer-related hypercalcemia.

The conduct of international research further contributes to a new understanding of the relationship between diet and cancer. Many studies conducted abroad are focusing on the same variables being investigated in the U.S. For example, The Istituto Nazionale Tumori in Milan, Italy, is evaluating the synthetic retinoid HPR (N-4-hydroxyphenyl retinamide) in a randomized clinical trial involving stage I breast cancer patients. In Finland, a group is working with a U.S. counterpart to determine: (a) if either beta carotene or alpha-tocopherol supplementation is effective in preventing lung cancer in smokers; (b) the role of selenium, vitamins A, E, and C, and fat in breast cancer; and (c) the roles of various levels of nutrients in subsequent cancer development.

Another contract has been awarded to conduct an intervention study in Linxian, China. This study will use multiple vitamin-mineral supplements containing beta carotene to evaluate the etiologic role of supplements in reducing esophageal cancer incidence.

The NCI also continues to support Clinical Nutrition Research Units at the University of Alabama and Memorial Sloan Kettering where all facets of nutrition related basic research are being undertaken.

The National Heart, Lung, and Blood Institute supports nutrition research in three major disease areas: heart and vascular diseases, blood diseases, and pulmonary diseases. A major portion of this research involves the role of nutrition in hypertension, atherosclerosis, and coronary heart disease. The role of nutrition in sickle cell disease, respiratory disease syndrome, and pulmonary function are also being investigated. The nutritional aspects of heart, lung, and blood diseases are supported across the biomedical research spectrum in basic research, applied research, clinical investigations, clinical trials, demonstration and education programs and research training.

The longitudinal studies of coronary heart disease risk factors in young adults (CARDIA) is a prospective epidemiological investigation of the precursors and determinants of CHD risk factors and their evolution over time in a biracial cohort of young men and women (ages 18-30 years). The principal objectives of these studies are: 1) to measure the prevalence and distribution of risk factors in this population (i.e., lipids/lipoproteins, blood pressure, smoking, adiposity) that have been related to the development of CHD in older cohorts; and 2) to identify lifestyles which influence these changes in risk factors. There are four clinical centers, a Data Coordinating Center, and four laboratories to quantitate lipids, lipoproteins, and apoproteins, blood chemistries, saliva cotinine and serum insulin. Fifty-one hundred individuals will be randomly selected from the community with adequate representation of all age-race-sex specific strata. The exam protocol includes phlebotomy, blood pressure, personal and family history, demographic information, several psychosocial inventories including a type A/B structured interview, a quantitative food frequency dietary instrument, pulmonary function testing, anthropometry and physical activity measures as well as a graded maximal exercise test. This exam will be readministered 2 years later to quantify changes in lifestyles and risk factors that have occurred in the intervening period. The protocol has been completed and the field operations are under way.

Several activities in cardiovascular/nutrition research are aimed at clarifying the role of dietary components in altering the atherosclerotic process. Basic research studies consider the effect of diet and heredity on the structure and function of lipoproteins; on the metabolism of lipids, lipoproteins and apolipoproteins as well as the progression and regression of the atherosclerotic plaque process; and on the relationship of abnormal carbohydrate metabolism to endogenous hypertriglyceridemia. Specific mechanisms for the control of cholesterol synthesis by the liver are under investigation, i.e., the possible role of hormones, cholesterol, cholesterol esters and other cholesterol metabolites are being evaluated in terms of their effect on the rate of cholesterol synthesis by the liver.

Short-term investigations and epidemiologic studies suggest that fish oils contain fatty acids which may be metabolically unique and may be antiatherogenic. Diets rich in omega-3-fatty acids have lipid lowering activity promoting lower levels of plasma cholesterol, low



density lipoproteins, triglycerides and very low density lipoproteins. The omega-3-fatty acids are also associated with increases in bleeding time and decreases in platelet aggregation. Current research support includes studies in both humans and animal models. The further definition of the effects of omega-3-fatty acids is being investigated in animal models. The human nutrition research studies of dietary omega-3-fatty acids include the following areas: mechanisms of the hypolipidemia effects; the efficacy and possible toxicity; and platelet and prostaglandin effects.

Community health education demonstration and intervention projects apply much of the knowledge gained from the epidemiological and basic research studies, and examine the effect of nutrition education on changes in dietary habits and the subsequent prevention or modification of cardiovascular disease risks. For example, nutrition intervention studies under way in the workplace, in clinical practice, and in school systems investigate the role of suggested dietary changes in lowering blood cholesterol, low density lipoproteins, triglycerides, and blood pressure. These changes in risk factors are then considered in terms of the possible prevention and control of hypercholesterolemia, atherosclerosis, and hypertension. Research continues on the development of appropriate nutrition education programs and adherence strategies that help to reduce the diet-related risk factors for hypertension, obesity, and cardiovascular disease.

Dietary intervention studies attempt to determine the success of controlling blood pressure by nonpharmacologic means such as through weight loss and decreased sodium intake; to assess changes in peripheral vascular resistance in response to dietary potassium and sodium such as the increased resistance with sodium in the hypertensive individual; to understand the relationships of dietary sodium and potassium to urinary prostaglandin excretion in terms of the etiology of hypertension; to examine renal humoral agents and the renal handling of sodium; and to develop quantitative methods for estimating sodium intake by measuring the excretion of sodium.

Research on nutrition's role in sickle cell disease and in thrombosis receives support from the NHLBI. Research on sickle cell disease aims to define the effect of various nutrients on red cell physiology, as well as the contributions of vitamin and mineral deficiencies to growth retardation and immunologic function in patients with the disease. Studies on thrombosis and hemostasis investigate the role of dietary lipids on platelet structure and function. Another study investigates the role of vitamin E on platelet aggregation and fluidity of the platelet membrane.

Respiratory distress syndrome (RDS) is the single most frequent cause of death during the neonatal period. Research in this area includes studies on maternal nutritional status as a means of reducing the risk of premature birth and subsequent risk of RDS. Two new binding proteins, one for retinol vitamin A and one for retinoic vitamin A, are being examined during perinatal development in terms of their role in the maturation of lung tissue. In addition, investigators are considering the influence of nutrition on lung defense

functions such as the pulmonary alveolar macrophage and lung anti-oxidant enzymes. Since individuals with chronic obstructive lung disease are often malnourished, studies are under way to explain how malnutrition influences resistance to pulmonary infections, respiratory muscle fatigue, and lung surfactant function. In addition, vitamin C is being studied in terms of its role in the prevention of bronchoconstriction in patients with asthma and bronchitis.

As a followup to the findings of the Lipid Research Clinics' Coronary Primary Prevention Trial, the NHLBI planned a number of activities. In June 1984, a workshop for both LRC and non-LRC investigators was held in order to examine the CPPT data in more depth, and to place these findings in relation to other clinical and epidemiological findings on this issue. Further implications of the results of this clinical trial were explored at the NIH Consensus Development Conference, "Lowering Blood Cholesterol to Prevent Heart Disease," held on December 12-14, 1984. The Consensus Development Conference addressed the issues relating to the use of diet and drugs in the lowering of blood cholesterol in an attempt to develop guidelines for health professionals and the lay public regarding cholesterol levels in different age and sex groups that should be treated, and the ultimate goals of treatment.

In August 1984, the NHLBI began planning for a National Cholesterol Education Program (NCEP). The NCEP will consist of cholesterol-lowering programs for health professionals, their patients, and the public to increase their awareness of the importance of lowering elevated blood cholesterol levels, and to provide the necessary information and skills to use dietary changes and drugs to accomplish this task. Such programs will also be established, as well as incorporated into workplace wellness or disease prevention programs. In addition, attempts will be made to increase the awareness of primary and secondary school students on the role of diet in preventing heart disease by means of the school curriculum and to reach special audiences, such as minority groups, through the development of materials and programs responsive to their specific needs. The mission of the NCEP is the reduction of CHD morbidity and mortality attributed to elevated blood cholesterol.

The NCEP will operate as a partnership with a wide range of organizations and through extensive cooperation and coordination with other government agencies and intermediary groups in the private sector. In order to mobilize, educate and coordinate the resources and energies of all interested groups, a coordinating committee for the NCEP will be established that may eventually consist of approximately 20-30 organizations that offer mutual support and guidance for the program. The committee will examine critical issues, consider future opportunities and directions, and facilitate collaboration among the member organizations.

A series of planning workshops to identify program elements and develop implementation strategies to reach defined target audiences or settings are scheduled for FY 1985. These workshops which will include representatives from selected organizations/agencies and NIH

staff will address the following major areas of program activity: professional and patient education; public education; worksite programs; and school and youth programs.

The National Institute of Dental Research supports research on the relationship between diet and nutrition, and the development and maintenance of both hard and soft tissues of the oral-facial complex. Special interests are in the problems of tooth and gingiva development and maintenance, periodontal diseases, and dental caries. NIDR's National Caries Program focuses on the development of a measure of the cariogenicity of various foods; the relationship of human diet to caries development; the identification and isolation of naturally occurring noncariogenic sweeteners and possible sucrose substitutes; the effects of sucrose substitutes with low cariogenic potential on growth, acid production and polysaccharide synthesis by oral bacteria; and the development of a slow release oral fluoride device, and fluoride mouthrinses and tablets. The role of fluoride in preventing dental caries has been established and NIDR continues to study the metabolic effects of various fluoride levels in humans, especially the effect of fluoride given prenatally and the mechanisms by which fluoride induces caries resistance in the child. Severe dental fluorosis is also under investigation.

In addition, studies are under way on the cellular and biochemical roles of vitamin A in the proper calcification of bone and dentin, the effects of various dietary lipids (saturated and unsaturated fats, cholesterol, and trans fatty acids) on salivary gland plasma membrane lipid composition, fluidity, enzyme activities, and saliva composition, and the effects of zinc deficiency on the stimulation of activity of epithelium lining in some regions of the oral cavity.

The National Institute of Arthritis, Diabetes, and Digestive and Kidney Diseases supports basic and clinical nutrition research that focuses on the function and requirements of specific nutrients, and the relationship of these nutrients and overall diet to health promotion, disease prevention, and disease treatment. In general, basic research on the metabolism of nutrients and their interactions deals primarily with specific nutrients rather than a particular disease, organ, or stage of life cycle.

Studies are under way on the metabolic role of specific dietary components, i.e., the essential amino acids and protein, carbohydrates, essential fatty acids and other lipids, vitamins, minerals, and dietary fiber. For example, tryptophan, tyrosine, and choline are being studied for their role in the formation of the neurotransmitters (serotonin, dopamine, and acetylcholine, respectively) as well as the subsequent effects on blood pressure, depression, and tardive dyskinesia. Noninvasive stable isotopes are being used to study the effect of dietary protein and energy intake on whole body amino acid metabolism with particular emphasis on alanine, glycine, and leucine. This research has opened up new approaches to estimating the amino acid requirements of healthy adults. Investigators are also studying the transport of peptides in the small intestine and kidney. Studies of fat metabolism examine the mechanisms of gastro-



intestinal fat digestion and absorption; the effects of dietary fat in the modification of microsomal chain elongation of fatty acids and thereby the fatty acid composition of tissue lipids; and the role of essential fatty acids in the diet on the regulation of bile acid synthesis and the formation of very low density lipoproteins.

Research on the fat soluble and water soluble vitamins attempts to clarify the mechanisms of metabolism and transport of vitamin A and its analogs, vitamin D and its metabolites, vitamin E, vitamin K, cobalamin, folate, thiamin, vitamin C, etc. For example, studies on the metabolism of vitamin A attempt to identify and isolate its metabolites and examine their roles in the maintenance of epithelial cells and keratinization of the skin. Studies on vitamin D examine its role in bone physiology in terms of its effect on calcium and phosphate absorption, as well as the hepatic regulation of vitamin levels during pregnancy. The mechanisms of folate absorption and utilization and folate binding proteins are investigated in order to develop a clearer understanding of folate deficiency states during pregnancy, in patients with intestinal diseases, in alcoholics, and in cancer patients. Studies of vitamin C attempt to establish appropriate levels of the vitamin for the treatment of osteoarthritis.

Studies on the trace minerals, i.e., iron, zinc, selenium, copper, silicon, chromium, tin, iodine, aluminum, molybdenum, magnesium, calcium, and phosphorous, provide important data on their metabolism, interrelationships, and overall relationship to human health. Imbalances or inadequacies of certain trace minerals are likely to promote metabolic adaptations that lead to chronic disease. Research continues on the biochemical basis of calcium absorption across the small intestine and the mechanisms of its regulation by vitamin D, dietary calcium, growth and aging, etc.; the bioavailability of iron in foods and iron deficiency, particularly in terms of work performance and exercise capacity, as well as changes in the red blood cells; and the mechanisms of transferrin's function as an iron donor or acceptor in liver cells. Zinc status of certain segments of the population may reflect dietary inadequacies. Studies are under way to establish the use of saliva for the assessment of zinc status. Studies on dietary fiber examine its effect on stool transit time, digestion, rate of absorption, intestinal microflora, and interactions with nutrients, drugs, bile salts, and other substances.

Fundamental research on the mechanism of action of nutrients in absorption and metabolism, biological control of these processes, and the identification of other possible roles of nutrients and their metabolites provide important insight into the role of diet in the etiology of major diseases. Studies on the effect of diet on amino acid metabolism are particularly concerned with examining the mechanisms associated with the alterations of the metabolism of the branched chain amino acids found in liver failure, trauma, renal disease, urea cycle defects, diabetes, and starvation. Metabolism of sulfur amino acids is of particular concern in cases of homocystinuria, alcoholic liver disease, chronic liver disease, and neuropsychiatric disorders.

The clinical investigations supported by NIADDK relate to the assessment of nutritional status, the use of various nutritional support modalities, total parenteral nutrition, nutrient-drug interactions, and various diseases or conditions such as obesity, diabetes, osteoporosis, anemia, atherosclerosis, end-stage renal disease, and alcoholism. Studies on the effectiveness of total parenteral nutrition examine its effects on hormone levels and gastric secretions in patients; on protein and fat metabolism and the utilization of  $N_{15}$  as a tracer for protein metabolism and synthesis rates; and on calcium metabolism and bone disease in patients with gastrointestinal problems.

A major research priority of NIADDK is the investigation of the underlying causes of obesity with particular emphasis on prevention and control. Studies investigate the regulation of fat cell size and fat metabolism; total body composition; fuel mobilization and storage; the effects of meal pattern, diet-induced thermogenesis, and exercise on energy metabolism; thyroid function and thermogenesis; the factors affecting appetite, hunger, and diet selection; behavioral techniques for weight loss; and behavioral and genetic correlates of obesity. Studies on the biochemical and physiological mechanisms for the control of food intake examine the role of specific amino acids and other nutrients, as well as the role of insulin, the central nervous system, and the gastrointestinal hormone, pancreatic polypeptide, in the regulation of appetite and weight control in obese and in normal weight individuals. Other investigators examine the patterns of eating in the lean and the obese individual, the effects of under and overnutrition on changes in thyroid function and catecholamine metabolism and the resulting effects on thermogenesis, and the metabolism of brown adipose tissue in terms of its effect on the regulation of energy balance and dietary induced thermogenesis. Determining the optimal diet, as well as the role of exercise and behavior modification techniques such as monetary incentives, for the treatment of obesity is an important component of this research, particularly in the treatment of obese children.

The U.S. Malnutrition Panel of the U.S.-Japan Cooperative Medical Sciences Program continues to be administered by NIADDK. The nutrition research fostered under the program investigates protein calorie malnutrition, and iron and vitamin A deficiencies. Solutions to these problems are primarily targeted to the undernourished populations of Asia and the Pacific Basin.

The NIADDK supports five Clinical Nutrition Research Units; namely, those located at the University of Chicago, University of Wisconsin, Vanderbilt University, the Medical College of Georgia, and Columbia University. The CNRU mechanism is stimulating progress in a multidisciplinary approach to clinical nutrition research, enhancing patient care, strengthening training environments in nutrition for medical students and other health professionals, and generating nutrition information for the public.

The National Institute of Neurological and Communicative Disorders and Stroke supports research on the mechanisms by which the structure and function of the neuron and synapse affect neuromuscular feeding

behaviors in animals, e.g., swallowing; the role of the brain in mediating acquisition, extinction and aversion of associations to gustatory, olfactory, and trigeminal stimulation; the electrophysiological activity of the brain resulting from changes in food intake in animals, as well as gustatory, olfactory, and trigeminal stimulation; neuroanatomical pathways connecting the gastrointestinal system to the hypothalamus, and the effect of changes in the gastrointestinal system on electrophysiological activity in the hypothalamus; neuroanatomical organizations and pathways of the somatic and autonomic nervous systems that control food intake and the behavioral, hormonal and metabolic mechanisms by which such pathways influence body weight; abnormalities in the brain of genetically obese animals; and neurological mechanisms of taste and smell, and their common chemical reception and chemosensory stimuli in a variety of animal models.

Nutrition studies in molecular biology, hemodynamics, and immunochemistry of the nervous system form the basis of many clinical investigations. Studies are being done on the effect of food additives, especially lipophilic acids, on the growth and differentiation of human cells in culture, and on vitamin requirements of bacterial and mammalian cells during differentiation and specialization. Studies in rhesus monkeys are looking at the effects of protein-calorie malnutrition during pregnancy on possible sensory, pathological, immunological and biochemical disturbances in the infant; various studies consider dietary manipulations and dietary habits in persons with hereditary metabolic disorders that can cause neurological abnormalities. Dietary manipulations are being studied in patients with transient or definite strokes who have either type two or type four hyperlipoproteinemia; studies on abnormalities in gastrointestinal absorption and hereditary sensory neuropathy; and in children, on the treatment and control of seizures with high fat diets. In collaboration with the World Health Organization, epidemiological studies in less developed countries are looking at nutritional factors in relation to nervous system disorders.

Studies are underway to examine the dietary and metabolic factors that effect the two-way interaction between the intake of neurotransmitter precursors, the neurotransmitters that result, and the function of the central nervous system; and to consider the mechanisms of nutrient transport across the blood-brain and blood-cerebrospinal fluid barriers as they influence the role of neurotransmitters in normal and abnormal brain metabolism.

Investigations to better define the effects of protein calorie malnutrition on central nervous system metabolism are being carried out along with basic studies to investigate the effects of nutritional deprivation on the development of biochemical alterations linked to changes in the higher cognitive functions of learning, memory, and psychosocial behavior throughout the life span. Studies are underway to explore the relationship between vitamins (e.g., vitamins B<sub>12</sub>, A, and C) and/or trace elements (copper, potassium, and selenium); and the physiochemical functions of the central nervous system, as well as the psychological higher functions of cognition and memory. Other studies examine the effects of various nutrients on chemosensory



dysfunction through the course of the natural history of dementias and other degenerative processes of the central nervous system (e.g., amyotrophic lateral sclerosis, multiple sclerosis, and myasthenia gravis, etc.); attempt to clarify the role of the central nervous system in the etiology of obesity through examinations of the neurophysiology and neurochemistry of ingestive behavior (i.e., appetite, feelings of hunger, satiety, eating, drinking, tasting, smelling, etc.); consider the relationship between obesity and stroke, i.e., whether obesity per se is a risk factor for stroke or is associated with other risk factors for the disease; attempt to elucidate the intermediary mechanisms modulating the effect of diet on atherosclerosis, and its impact on the natural history of cerebrovascular disease.

Studies are examining the effects of central nervous system trauma on carbohydrate, fat, and protein metabolism in order to determine adequate dietary interventions needed to restore nutritional status and thereby minimize damage and accelerate recovery; investigating the relationship between dietary habits of various primitive cultures and the incidence of slow virus infections, such as Creutzfeldt-Jacob disease, Alzheimer's disease and amyotrophic lateral sclerosis; and considering the metabolic effects of nutrients on the inborn errors of metabolism associated with neurological impairment and the influence of nutrients on the onset or progression of other neurological disorders. The role of lysine and its metabolites are being examined in relationship to sedation, sleep, and other neuronal functions associated with neurological disorders. Acute and chronic hyperaminoacidemias are being studied in terms of their effects on the regulation of amino acid and protein metabolism in the brain. Other studies are looking at the dietary and metabolic factors that contribute to the growth, development, and overall health of the somatic (central and peripheral) and autonomic nervous systems.

Attempts to clarify the two-way interaction between nutrient intake and function of the central nervous system include studies on the effects of protein-calorie malnutrition and vitamin deficiencies on central nervous system metabolism and fetal development; the effect of plant and synthetic neurotoxins on the molecular and cellular mechanisms that underlie neuronal development, maintenance, degeneration and regeneration; and the molecular mechanisms of neurotransmitter release, i.e., through changes in membrane lipids and calcium flux across the membrane as well as in conditions of vitamin deficiencies.

Basic studies examine the neural control of ingestive and drinking behaviors and the effect on appetite of the interaction between gustatory sense and olfaction. The role of zinc deficiency on disorders of taste and smell is under investigation, as well as the role of active and passive ion transport in taste and the effects of hormones and various metabolic factors that may govern food preferences and intake. Investigators attempt to define the neural substrates through which gustatory afferent information elicits either ingestion or rejection of food in the oral cavity, as well as examine the peripheral modulatory influences on lateral preoptic,

lateral hypothalamic, and thalamic taste nucleus neurons, and relevant neurotransmitters involved in ingestive behaviors. A particular neuropeptide cyclo-(His-Pro) is being examined as a physiological modulator of normal appetite regulation since it has been shown to produce satiety; the effect of diet on hormonal and metabolic regulations of ingestive behavior, energy homeostasis and expenditures, and weight loss is an important component of this research.

The role of the central nervous system, particularly the monoamine, norepinephrine, on energy homeostasis is being examined in terms of the occurrence of spontaneous obesity. Results from such studies are important for the prevention and treatment of obesity through various means including the development of anorectic agents used to control overeating. Studies are being carried out on the relationship between hypercholesterolemia and disturbances in auditory function, i.e., whether hypercholesterolemia affects auditory function and structure directly, or if, with hypercholesterolemia, the ear merely becomes more susceptible to damage from occupation or environmental noises. Other investigators examine the role of nutrition in cerebrovascular disease and stroke, and in post-traumatic epilepsy. Of particular interest is the use of intracerebral injections of aqueous solutions of ferrous or ferric salts in the prevention of post-traumatic epilepsy.

The National Institute of Allergy and Infectious Diseases promotes and supports research in the broad field of nutrition, infection, and immunity. Important research efforts in this program are summarized in the following narrative.

Food allergy may play an important role in gastrointestinal disease, but little is known about the prevalence of food allergy, its mechanism of action, or its effect on gastrointestinal function. Recently an NIAID sponsored Food Allergy Working Group has been established whose mission is to develop clinical definitions, standardize the composition of food allergens, and conduct clinical trials of food allergens using standard protocols. The NIAID, in conjunction with the American Academy of Allergy and Immunology, published a monograph entitled Adverse Reactions to Foods. It covers allergic and other adverse reactions to foods. It tries to clear the air of the many myths in this area by presenting what is known about reactions to foods. In the past, food allergy had been dismissed as a factor in atopic dermatitis. However, NIAID-funded research in the past 3 years has shown that food allergy is a cause for skin symptomatology in up to one-half of a selected group of children with severe atopic dermatitis. Such increasing recognition of the role of food allergies in disease should lead to improved patient care and a decrease in medical expenses. Investigators are working to develop standard diagnostic tests to determine who may be at risk from allergic reactions to foods. Of children found allergic to a particular food, 60 percent lose their sensitivity if kept on a restricted diet for 1 to 2 years. Also, patients, in whom a food was identified as causing clinical symptoms and who avoided this food for several years, did better than a second group for which no food was identified or eliminated. These results show the importance of accurately identifying

food allergy and modifying the diet. Several NIAID-funded investigators are studying the mechanisms underlying food allergies. There is one report of a rise in plasma histamine, a chemical mediator of allergic reactions, following positive food challenges. Another investigator is looking at which antigens extracted from crustacea (shrimp, crab, lobster) are responsible for provoking an allergic reaction upon ingestion by allergic patients.

Studies examine the modulating effects of specific nutrients such as amino acids, vitamins, minerals, and fatty acids on basic immune functions. Of particular interest are the modulating effects of iron and related elements on microbial virulence.

Additional studies are under way on the effect of malnutrition on resistance to infections, especially infectious diarrhea in children; the role of breast milk in defense against enteric infections; and the effect of infections on nutritional status. Investigators are examining leukocyte mobility in neonates and malnourished infants, the influence of endotoxins on zinc and copper metabolism, synergistic host defense role of fever and changes in plasma iron and copper levels, the effects of protein and zinc deficiency alone and in combination on the efficacy of BCG vaccine, and the role of arachidonate metabolism in host defense and inflammatory reactions. Other research is concerned with the effects of parenteral and enteral nutritional support of the patient on their immune function and hospital infections.

Until recently, many pediatricians in the United States were reluctant to use oral rehydration solutions (ORS) containing "high" concentrations of sodium for fear of inducing hypernatremia (an excess concentration of sodium in blood) in children with diarrhea and dehydration. In FY 1984, investigators at Johns Hopkins University, supported in part by NIAID, conducted a controlled clinical trial in U.S. children and concluded that ORS containing "high" concentrations of sodium can be used safely for the treatment of mild, acute diarrhea and citrate. ORS is as efficacious as bicarbonate in the correction of acidosis. Citrate has a longer shelf life than bicarbonate. Thus, citrated solutions are more practical. Recent studies have demonstrated that in infants with acute diarrhea, the volume and duration of diarrhea can be reduced dramatically by using an ORS containing hydrolyzed whey protein. It has been observed that hydrolyzed whey protein improves sodium resorption from the gut, reverses the secretory process, and thereby reduces diarrhea. The favorable antidiarrhea effect of whey protein ORS probably results from its high content of amino acids which help to promote fluid and salt resorption by the bowel. It seems likely that in the future less expensive ORS made from rice that contains both carbohydrate and protein will be developed not only to replace the fluid and electrolyte loss, but at the same time to decrease or stop the diarrhea entirely in children suffering with acute infectious gastroenteritis in developing countries.

The National Institute of General Medical Sciences supports research directed to the discovery of better ways to prevent death from inju-



ry, mitigate pain, speed recovery of patients, and lessen the extent of disabilities caused by injuries. A better understanding is sought of the total body response to trauma, including burns. Studies are under way on the biochemical and physiological changes induced by trauma, and the fundamental aspects of wound healing and biological repair. For example, investigators are examining the sympathetic regulation of fat metabolism during sepsis; amino acid release from skeletal muscle and differences in control mechanisms following stress and trauma; hepatic glucose metabolism during shock; and physiological and biochemical alterations in specific organs such as the liver, which are initiated and integrated by neuroendocrine mechanisms used for the maintenance of homeostasis during shock.

Emphasis is also given to research on the treatment of post-traumatic infections, nutritional requirements of burn victims, and rehabilitation of injured patients. The NIGMS trauma and burn program supports research related to nutrition in the following areas: nutritional aspects of severe trauma and sepsis, new concepts in parenteral protein sparing therapy, branched chain amino acid feeding during injury, and cellular response in shock. The therapeutic value of fructose 1-6 diphosphate is being evaluated for treatment in several types of shock, i.e., hemorrhagic, endotoxin, tourniquet and burn shock. The effects of parenteral nutrition, especially the use of medium chain triglycerides, on the oxidation of fuel, protein synthesis and storage in the critically ill traumatized patient and septic patient, as well as on impaired cellular function and immunity in patients after surgery and trauma are also being studied. In addition, because diabetics appear to be more susceptible to sepsis, investigators are interested in the causative factors for major metabolic alterations in these patients that create a greater reliance on exogenously administered insulin. Data from this research will help to develop specific therapeutic modalities for the treatment of the diabetic patient with bacterial infections.

The National Institute of Child Health and Human Development research program focuses on the continuum of human development, from conception through infancy, childhood, and adolescence. The program emphasizes preventive approaches to nutrition-related conditions and stresses health promotion as well as disease prevention. Much of the research is multidisciplinary in nature and involves genetic, biochemical, developmental, anthropometric, behavioral, and cultural aspects of nutrition.

The NICHD has a strong interest in the area of maternal and infant nutrition and in elucidating the roles played by diet in infant development. Research interests focus on the nutrient requirements of normal, premature, and growth retarded infants, as well as on the composition of human milk, cow's milk, and synthetic formulas in relation to optimal infant nutrition. In some of this work, the interest centers on metabolic processes in neonatal adaptation, and on the role played by essential nutrients and other components of human milk in optimizing early development. Studies are under way on the amount and type of vitamin D metabolites required by the low birth weight infant and other neonates at various gestational ages,

as well as on the interrelationships of the essential, exogenously derived, hematologic nutrients of tocopherol, selenium, iron, folate and vitamin B<sub>12</sub> in the premature infant. For example, investigators examine the clinical and immunological status of premature newborns on diets with or without supplemental vitamin E, since this vitamin is important for the prevention of hemolytic anemia of prematurity, retrolental fibroplasia, and bronchopulmonary dysplasia. Other investigators examine the cellular factors that define or limit skeletal muscle growth potential and attempt to elucidate the mechanisms by which postnatal undernutrition may cause permanent growth retardation of skeletal muscle.

In order to assure optimum development in children, adequate nutrition should be provided to them in utero. Research continues to examine the complex relationship between the mother and her fetus in terms of nutrient transfer across the placenta, and to ascertain the effects of excessive or deficient amounts of certain nutrients on the morphologic and endocrine development of the fetus. Of particular interest is the placental transfer of oxygen, amino acids, vitamin A, iron, and folic acid. Studies have shown that dietary deficiencies of protein as well as of vitamin A in the mother cause fetal abnormalities in vitamin A metabolism, while deficiencies of iron in the mother also adversely affect the placental transfer of iron which is vital to fetal growth. Marginal deficiencies of folic acid during pregnancy are being examined in terms of its effect on growth and folic acid status of the newborn. Other investigations are under way to examine the effects of intrauterine malnutrition on neonatal lymphocyte function and the correlation between lymphocyte function and the risk of neonatal infections. Studies also are concerned with the relationship of serum folic acid levels of the mother on the etiology and prevention of neural tube defects, cranium bifidum and spinal bifida of the newborn, as well as the interaction of folate with zinc in fetal alcohol syndrome. Other studies of fetal alcohol syndrome examine the effects of small doses of ethanol on morphology, morphometry, and functions of the hippocampal brain regions in zinc deficient animals. Calcium metabolism is also examined during pregnancy in terms of its hormonal control and its effects on intrauterine growth and postnatal development of the infant.

Most studies on nutritional aspects of developmental gastroenterology consist of basic research on cellular differentiation in relation to the functional development of the gastrointestinal tract. Human milk appears to provide specific components that stimulate functional development of the newborn's intestinal tract as well as digestive enzymes, such as lipases, which the infant is unable to produce in sufficient quantities. Studies examine carbohydrate tolerance of the infant by measuring the pulmonary excretion rate of hydrogen gas as an index of the functional capacity of the intestine to effectively utilize breast milk and commercial infant formula that contains the disaccharide lactose. Other investigators are studying the ability of infants between birth and 1 year of age to utilize starch through the development of salivary and pancreatic alpha-amylase and intestinal glucoamylase. The effects of various feeding methods and diets (cows' milk, soybean base, elemental formula, and total parenteral

nutrition) on the development of pancreatic and salivary amylase are also examined. Studies are also progressing on digestive and absorptive disorders during infancy, particularly intractable diarrhea.

Studies on human milk and colostrum emphasize the conveyance of passive immunity to the young infant; the roles played by specific components of milk in stimulating cerebral and gastrointestinal development; the effect of maternal factors such as age, parity, nutritional status and duration of lactation on the composition of breast milk and colostrum; and neural and hormonal regulation of lactation. Research interests include the relationship of protein intake and trace metals to cerebral growth and function; the effect of nutritional deficits and excesses on physical growth and maturation; and the effect of nonnutritive food components, such as toxins, allergens, and contaminants, on the growth, development and health of children.

Studies are under way to examine the potential beneficial role of leukocytes present in human milk as well as other components that mediate the uptake of bound folate in the intestine of breast-fed infants. Investigators also attempt to isolate the intestinal receptor for the factor in breast milk that enhances folate absorption. Studies of the possible benefits and drawbacks of feeding the low birth weight infant with human milk versus infant formula consider the biochemical evidence of protein sufficiency or excess from both types of feeding in terms of the overall nutritional management of these infants. Another study evaluates the physical growth, immunological development, and gastrointestinal function of low birth weight infants fed human milk versus formula. Other studies examine the differences in the lipoprotein bile salt stimulated lipase activities and the macronutrient and electrolyte content of mature and preterm breast milk. The taurine, carnitine, and other amino acids in human milk are of particular interest, as well as the quantity, distribution, and morphology of plasma membrane materials present in human milk. A major contract is developing human milk banking technologies for collection, storage, processing, and distribution of human milk and colostrum. The goal is to discover ways to preserve the labile nutritional and immunological components of human milk and colostrum during processing and storage.

Studies evaluate the antecedents and determinants of infant feeding practices; the frequency and duration of infant feeding practices of primiparae; the effects of westernization on feeding patterns among nomadic populations; the frequency and types of illnesses in infancy and early childhood as well as weight gain, physical growth, and behavioral characteristics as expressions of mother-child interactions in breast-fed versus formula-fed infants; and the relationship of maternal diet, alcohol and tobacco use during lactation to the physical and psychological growth and development of the infant. An epidemiological study is examining the relationship between types of infant feeding (human milk, cow's milk, or commercial formula) on serum cholesterol levels of children between the ages of 4-11 years. This study is testing the hypothesis that the high cholesterol content of breast milk establishes a homeostatic mechanism that allows



for effective cholesterol metabolism in adult life. Other variables tested in the children include the effects of current age, sex, race, parental income, parental education, current weight, current diet, and age of introduction of solid foods on the relationship between type and duration of infant feeding and childhood serum cholesterol levels.

Research on dietary therapy of inborn errors of metabolism looks at abnormal metabolism of nutrient substrates. Included are investigations of the biochemistry and genetics of inborn errors which are, or may prove to be, treatable with diet. Many inborn errors of metabolism cause mental retardation or other disabilities of the central nervous system. Clinical research has shown that some of these diseases are amenable to nutritional management, as are a number of inherited metabolic diseases not associated with mental subnormality, such as lactase deficiency, cystic fibrosis, and some hereditary anemias. In most inborn errors of metabolism, the mechanisms by which aberrant levels of metabolic intermediates interfere with cerebral function remain unknown; neurochemical research in animal models, e.g., experimental phenylketonuria and galactosemia, is being supported to answer this central question. One study of PKU is examining the point in time in which the initiation of diet therapy restricting phenylalanine can prevent the mental retardation, and physical and neurological growth changes in infants that occur with this inborn error of metabolism. Another study of maternal PKU investigates the biochemical and behavioral indices of fetal cerebral development in a normal and phenylketonuric environment, i.e., behavioral tests are selected to determine whether any of the biochemical abnormalities resulting from the simulated maternal PKU are associated with a delay in functional development, deficits in cognitive functions (spatial and memory), and changes in noncognitive behaviors (behavioral arousal and response inhibition).

Another study attempts to determine if iron therapy can correct the developmental deficits and behavioral abnormalities associated with iron deficiency anemia of infants. Investigators have shown a strong relationship between abnormal behavior, poor test performance, and impaired cognitive function in iron deficient, anemic infants. Further studies attempt to determine the level of iron depletion at which infant behavior is adversely affected; any differences between injectable and oral iron supplements on behavior; and whether iron therapy can correct the deficits and confirm specific patterns of behavioral disturbances. Results from this research will help to determine and develop preventive strategies, screening priorities, the level of iron deficiency requiring treatment, and the most efficient therapy for iron deficiency anemias.

Research on cultural and behavioral determinants of nutritional individuality includes studies of habits, taste and olfaction; food avoidances; and behavior modification of dietary intakes. Research on nutritional antecedents of adult disease focuses primarily on factors in the development of obesity in infancy, childhood, and adolescence. Behavioral, neurochemical, genetic, and hormonal factors involved in obesity are under investigation; the psychosocial

and nutritional aspects of both adolescent obesity and anorexia nervosa are being studied. Studies examine the control of ingestion, appetite, and regulation of body weight in normal and obese infants. Obese children having one or two obese parents are being studied for energy balance, eating and exercise habits, self-evaluation skills and behavior patterns. Childhood obesity is also being studied in terms of its association with earlier eating and physical activity practices and parental attitudes. Examinations of resting metabolic rates, daily energy expenditure, and the thermogenic and hormonal responses to overfeeding are under way in obese adolescents. Changes in body composition and comparisons of energy expenditure help to clarify whether obese adolescents can dissipate excess calories derived from carbohydrate in the same way as the non-obese. Studies are under way to clarify whether fat or carbohydrate is the most appropriate source of energy for supporting the growth spurt in obese adolescents receiving hypocaloric dietary therapy and to determine if weight reduction in obese adolescents results in normalization of protein and glucose metabolism.

Since the patterns of adolescence usually persist into adulthood, and long-term consequences of eating behavior may involve diseases related to lifestyle such as heart disease, diabetes, hypertension, and cancer, studies are under way to examine the cognitive, developmental, social, and environmental factors that affect the processes that determine the patterns of food consumption during adolescence. Other investigations are under way on the complex relationship of malnutrition and social and health factors that affect the psychological development of children. These studies on the effects of malnutrition and environmental deprivation in child development hope to establish the extent to which it is possible to prevent retardation of physical and psychological growth by food supplementation and maternal tutoring. Studies also examine nutrition's role in diabetes in pregnancy and among infants of diabetic mothers. Studies on the physiology and pathophysiology involved in the diabetic pregnancy permits a rational approach for decreasing fetal and neonatal deaths and morbidity in the offspring of the diabetic.

Other NICHD research emphasizes the development of new methods for assessing nutritional status, particularly during infancy, adolescence, pregnancy, and lactation. New noninvasive methods are being developed to measure serum ferritin, serum vitamin E, lactose absorption, and body composition. Mass spectrometric studies use stable isotopes of calcium, lecithin, and amino acids, while x-ray fluorescence spectroscopy and atomic absorption spectrophotometry are also being used.

Studies also investigate the effects of nutritional alterations on gonadotropin secretion, ovarian function and fertility. Research emphasizes the role of vitamins and minerals in sensitive reproductive processes (such as spermatogenesis), and the effects of oral contraceptives on the metabolism of folic acid, pyridoxine, and ascorbic acid. The reproductive consequences of low protein diets as reflected in gonadotropin production, fertility, and lactation are also under investigation.

The National Eye Institute supports research on the role of overall nutrition as well as specific nutrients such as vitamins A and E, protein, copper, and zinc, on normal ocular and visual development, health and function. Studies also examine the association between nutritional imbalances and eye and vision disorders such as cataracts, retrolental fibroplasia, retinitis pigmentosa, gyrate atrophy, and childhood blindness.

The role of vitamin A in the visual process, particularly in the generation and recycling of rhodopsin, is an important research area since vitamin A deficiency is the leading cause of blindness in children living in the developing world countries. Investigators are studying the interaction in ocular tissue of vitamin A with other nutrients such as vitamin E and zinc; the role of binding proteins for retinoids in ocular tissue compartments; and the factors that modify their synthesis and metabolism. Studies examine the molecular structure of retinol binding proteins and their function in the eye since deficiencies of the proteins or altered binding specificity and affinity for retinol affect normal functioning of vitamin A in the retina and the pigment epithelium of dystrophic eyes. The proteins specific for retinol, 11-cis-retinal and retinoic acid, are being investigated in terms of their interactions with enzymes, proteins, and compartments known to be important in the metabolism of vitamin A in ocular tissues. In addition, investigators attempt to characterize and purify the enzyme retinol isomerase which is important for the isomerization of 11-cis-retinaldehyde in rhodopsin to all-trans retinaldehyde, as well as to define possible links between isomerization and available energy systems, and to determine the mode of intercellular transfer of vitamin A from pigment epithelium to the rods.

Other studies examine whether postprandial changes in plasma amino acids, ethanol consumption, or diabetes influence the uptake of tyrosine and tryptophan at the retinal-blood barrier; tyrosine and tryptophan are the precursors for dopamine and melatonin respectively; both are important in the regulation of light sensitivity in the eyes. Differences in dietary protein and fat are also investigated in terms of how they alter ocular membrane structure and function. Of particular interest are alterations in membrane phospholipids that influence intercellular transport of calcium, copper, and zinc and its consequential effects on the visual process and the development of retinopathies.

Research findings have shown that pharmacological doses of specific nutrients, particularly vitamin E, may protect ocular tissue against various retinopathies. For example, vitamin E's role in reducing the incidence and severity of retrolental fibroplasia in the premature infant and in protecting the eye from the cytotoxic effects of accumulated natural or induced oxidants is being investigated. In addition, topical application or parenteral administration of ascorbate and citrate are being investigated in terms of reducing corneal ulcerations and perforations in the alkali burned eye. The use of an arginine deficient diet in the treatment of gyrate atrophy is also



an area of research. The corneal uptake and metabolism of topically applied retinoids are being studied in terms of efficacy of their use in the treatment of xerophthalmia and the promotion of corneal wound healing.

Studies are under way on the effect of specific nutrient deficiencies, such as vitamins A, E, ascorbic acid, riboflavin, tryptophan, and taurine, zinc, selenium, and copper, on the eye. Imbalances in these nutrients are being considered as possible risk factors for cataract development. Vitamin E deficiency is under investigation since it causes changes in the outer segments of photoreceptors and a buildup of autofluorescent pigment within the pigment epithelium; with time these may cause a total loss of photoreceptors and the appearance of autofluorescent pigment in all retinal layers. Zinc deficiency is known to have an adverse effect on vision due to an increased accumulation of electron dense inclusion bodies in the retinal pigment epithelium (RPE) cells, which, along with the photoreceptor outer segments, subsequently undergo severe degeneration. Dietary excesses of selenium have been shown to be related to an increased incidence of cataracts. Other studies on the development of cataracts investigate the relationship between changes in cations and water balance in the lens, the regulation of calcium levels in the lens, calcium's role in maintaining membrane permeability of the lens, and lens changes in experimental hypocalcemic cataracts. Investigations also examine the visual system's ability to recover from trauma in terms of the effect of specific nutrients on the ocular immune responses.

The National Institute of Environmental Health Sciences supports research on the biological risks and toxic adverse effects of environmental agents such as food-borne contaminants and additives on biological systems.

Food toxicology research examines naturally occurring products, such as those present as food plant components or mycotoxins (aflatoxins), as well as chemical agents intentionally introduced to foods as additives or unintentionally as environmental contaminants. Food toxicants and toxic alterations of the absorption, metabolic and excretory functions of the gastrointestinal tract are being investigated not only in terms of their role as biological stressors, but also to understand how the toxicant interacts with other environmental contaminants.

Studies attempt to determine the mutagenicity of food-borne toxicants to Salmonella typhimurium and to human lymphoblasts, and their carcinogenicity in rodents; the formation and detection of n-nitroso compounds and hydroxamates, products of pyrolysis of amino acids, proteins, and other food materials; and reaction products of peroxidizing lipids and cholesterol oxidation. The influence of diet on carcinogenicity of amino acid pyrolysis products and DNA damage caused by carcinogens in rat tissue is under investigation; and studies of aflatoxin B<sub>1</sub> carcinogenesis using the trout model are examining whether carcinogenesis can be inhibited by diet using biologically relevant doses and exposure patterns. Other studies of

carcinogens are concerned with the polycyclic aromatic hydrocarbon carcinogens (PAHC) that appear to cause increased proliferation and accelerated size increases in spontaneous fibrous lesions that appear to be precursors of atherosclerotic plaques. Cholesterol feeding is being tested as to whether it exacerbates the development of lesions and whether active protease inhibitors, retinyl acetate or aspirin, added to the diet interfere with lesion development. This research provides valuable information as to the promotional nature of the carcinogens, the early steps and processes associated with growth and development of spontaneous lesions, and the role of dietary supplements to modify the process of atherosclerotic plaque formation.

In addition, the effects of heavy metal intake on the metabolism and balance of essential elements are being examined. For example, studies are under way to investigate the consequences of long-term selenium intake and the possible adverse health effects of some selenium compounds; and the influence of diet and maturation of the intestine on the mechanisms of heavy metal absorption and distribution from the perfused lumen of the jejunum; and the accumulation of these metals in the jejunal mucosa (i.e., lead, cadmium, mercury, copper and nickel are being examined for metal interactions and for specificity of transport inhibitors). Chronic administration of lead is being investigated for its effect on absorptive functions of the gastrointestinal tract because it appears to be related to altered fecal output, increased urinary delta-aminolevulinic acid, anemia, and anorexia. In addition, cadmium and mercury are being studied in terms of their role in amino acid transport and renal function and in the development of nephrotoxicity. Additional studies seek to determine toxic changes generated in the enterohepatic, biliary, and renal systems by environmental contaminants and the alteration of these systems to prevent biological insults through decreased absorption and enhanced secretion. These studies hope to clarify how natural food products such as mycotoxins or their metabolites are generated in the body; the specific mechanisms of food toxicity; the interactions of food-borne contaminants with other environmental agents that increase or decrease toxicity; and the health risks associated with exposure to food contaminants.

Other studies investigate contaminants resulting from food storage generated under suboptimal storage conditions. Food processing hazards such as nitrites, nitrates, and other additives are being studied to learn how they are altered in the foodstuff and how they are transformed by biological systems. Studies also attempt to determine chronic effects of small concentrations of ozone on the metabolism of rats and mice in the presence of normal and high levels of polyunsaturated fatty acids in the diet, and in the presence and absence of vitamin E and DPPD, a synthetic antioxidant. The effects of ozone on vitamin E metabolism and of linoleic acid oxidation in vivo is of particular interest.

The National Institute on Aging supports basic and clinical investigations on nutrition's role in the aging process. For example, studies are under way on the effects of food restriction on increased life span, and the effect of nutritional status on immune function

and on the structure and function of several tissues, including adipose, hepatic, brain, muscular, skeletal, and vascular tissues. A variety of nutrient manipulations are being investigated in terms of their effects on longevity, as well as on the age of onset and nature of age-related diseases and changes in adipose tissue physiology, metabolism and hormonal components of blood serum, hepatic lipid metabolism, skeletal muscle function, functional properties of arteries, and bone loss. Protein undernutrition, in particular, is being examined in terms of possible neurochemical changes in the hypothalamus-pituitary-gonadal axis of rats with age. Other studies examine the effects of diet, especially that supplemented with the catecholamine precursor l-tryptophan, on ovarian function with age. Research continues to examine the normal nutrient requirements of the elderly, as well as requirements altered by disease or chronic drug regimens.

Studies on the effects that various age-related physiological changes may have on nutritional status focus on changes in renal physiology, intestinal physiology, taste and smell, salivary secretions, and dentition. Such physiological changes affect food intake and the digestion and absorption of necessary nutrients. It is thought that aging dulls the common chemical taste sense that registers the spicy and sharp components of substances like vinegar, salt, horseradish, carbonated beverages, as well as the sense of smell. Researchers are attempting to separate out true sensory losses from cognitive changes with age in order to develop ways to improve the pleasure of eating for the elderly and thereby possibly improve their nutritional status.

There is increasing evidence that nutritional factors may play a role in degenerative diseases of aging, including osteoporosis (low calcium and vitamin D intake) and Alzheimer's disease (trace metals). Zinc deficiencies in the elderly have been implicated in immune dysfunction leading to increased susceptibility to infection. However, definitive information on the role of these and other factors is lacking. In addition, the fact that most nutrients affect several physiological systems makes dietary requirements for the aging population especially unclear. NIA currently supports research on the role of nutritional factors in osteoporosis, age-related immune dysfunction, and Alzheimer's disease.

Also under investigation is the relationship between nutritional status and subsequent morbidity and mortality among the elderly in terms of such diseases as cancer, coronary heart disease, stroke, and osteoporosis. For example, studies address the role of vitamin D in calcium transport and subsequent bone turnover in postmenopausal women, as well as the effect of protein malnutrition on reduced immune function often found in the elderly. Variations in bone resorption and its effects on the rapid and dynamic relationship between the contribution of bone and diet to blood calcium levels are being quantified during various treatments with vitamin C, calcium, fluoride, etc. In addition, deficiencies of vitamin D, zinc, and folate have been found in several of the aged populations in the U.S. In light of these findings, investigators are studying why some elderly individuals have a decreased plasma level of 25-hydroxy-



vitamin D concentration and if this vitamin abnormality developed along with or independently of changes in calcium homeostasis. Researchers are also investigating the influence of age on the ability of the skin to photosynthesize adequate amounts of vitamin D<sub>3</sub>. Another study in animals of various ages is investigating the ways in which aging influences zinc metabolism and the response of the aged animals to suboptimal levels of dietary zinc. Folate deficiency is being studied in terms of decreased intestinal folate absorption with aging as well as the possible influence of drugs impeding folate absorption.

The Division of Research Resources provides support for important resources needed for the performance of research in nutrition. Many investigators funded by the categorical institutes of NIH for nutrition research use DRR's resources. DRR administers and manages five programs that serve health researchers at universities, hospitals, and research institutions throughout the United States. These programs are the General Clinical Research Centers, Biomedical Research Technology Program, Animal Resources, Biomedical Research Support, and Minority Biomedical Research Support. During FY 1984 all of these programs supported nutrition research.

The General Clinical Research Centers (GCRC) Program is composed of 75 specialized centers in major hospitals throughout the United States where more than 3,000 protocols are pursued annually by clinical researchers. The program supports 80 percent of all the inpatient care costs awarded by the NIH. In addition, an extensive outpatient activity is conducted within the existing centers. The range of studies related to nutrition, on both inpatients and outpatients, includes all aspects of research in nutrition, health, and disease. These centers conduct clinical nutrition studies on atherosclerosis, cancer, diabetes, environmental health factors, hyperlipidemias, obesity, parenteral nutrition, and vitamins. Two hundred and thirty-nine full-time dietary personnel are working on the GCRC's, and dietary interns spend training periods there. Most of the centers have a diet kitchen. The GCRC program is providing support for young clinical investigators who want to pursue a career in clinical research. Several of these clinical associate physicians are involved in clinical nutrition research.

The objective of DRR's Biomedical Research Support Program is to strengthen and enhance the research environment of institutions engaged in health-related research, through the use of flexible funds and local decisionmaking which enable them to more efficiently and effectively conduct their biomedical research programs. Appropriate uses of awarded funds include pilot research studies, support of new investigators, unexpected research requirements and emergencies, and central shared research resources.

The overall objective of the Animal Resources Program is to support resource projects that provide, or enable scientists to most effectively use, laboratory animals in human health-related research. The objective is accomplished through the Regional Primate Research Centers Program and the Laboratory Animal Sciences Program. Particu-

lar attention is given to animal resource activities that are supportive of the categorical interests of NIH. An important research area supported under this program is nutrition.

The Biomedical Research Technology Program uses specialized facilities and expertise in the physical sciences to create biomedically relevant technologies and to make these technologies accessible to biomedical scientists across the country. A number of these facilities are used to support research in nutrition.

The Minority Biomedical Research Support Program provides funds to institutions with predominantly minority enrollments. The funds are used to provide opportunities for minorities to participate in the conduct of biomedical research, some of which are in the area of nutrition.

In summary, the Institutes with mandates in categorical diseases support nutrition research programs in their areas of responsibility in both the prevention and the treatment of disease; namely, NCI on diet and cancer; NHLBI on diet and heart, lung and blood disorders; NIDR on nutrition and dental caries; NIGMS on nutrition and trauma including burns; and NEI on nutrition and various eye disorders. NIADDK, NICHD, and NIA support nutrition research particularly related to nutrient requirements relevant to the different stages of the life cycle and specific metabolic and genetic diseases. NINCDS supports research on nutrient intake and metabolic changes as these affect the nervous system in health (growth and development) and disease; NIAID on the role of nutrition on infection and immune system function; and NIEHS on the effect of environmental agents such as food contaminants and additives on biological systems. Through studies in biochemistry, physiology, and cell biology, NIH supported research aims to elucidate fundamental mechanisms in order to synthesize the results into practical information on nutrition and diet that will assist the individual to develop normally, and to live as long and as healthy a life as possible.

#### Manpower Development

Manpower development in nutrition research is enhanced through Research Career Development Awards (RCDA's) and New Investigator Research Awards (NIRA's). In FY 1984, 160 awards were given for a total of \$3,824,000.

Recipients of the RCDA awards conduct nutrition research in the areas of metabolism, human growth and development, nutrition and cancer, and cardiovascular and lung diseases. Examples of the studies in each of these areas are:

- o Metabolic studies include research on: metabolic and endocrine aspects of obesity; regulation of human gastric responses to meals; hypothalamic control of body weight and feeding; evaluations of dietary alterations and treatments; epidemiology of digestive diseases; neural and humoral control of mucosal transport; study of nutritional and hemolytic anemias; gastro-

intestinal digestion and absorption of fats; development and control of hepatic and renal gluconeogenesis; intestinal absorption of calories and minerals in man; metabolic role of cobalamin and folate; folate supply and utilization; protein nutrition in experimental uremia; calcium binding proteins and the vitamin D endocrine system; glycerol-3-phosphate dehydrogenase and egg yolk avidin; metabolic effects of burn injury and sepsis; the physiological role of esterified vitamin A in photoreceptor cells and the interaction between photoreceptors and pigment epithelial cells; resonance raman microscopy of visual photoreceptors; and the biochemistry of oral tissues, secretions, and diseases.

- o Studies on human growth and development include research on: nutrition and development of adipose tissue, i.e., lipoprotein lipase activity related to feeding behavior; the role of glucose production in the developmental maturation of neonatal carbohydrate homeostasis; developmental aspects of renal transport and experimental models of Fanconi syndrome; breath analysis for carbohydrate absorption in neonates; chemical studies in growth and development; nutrient transport in the developing intestine and colon; the appropriate forms and levels of vitamin D supplements for preterm and term infants; dietary habits during childhood and etiology of breast cancer or other diseases in later years; pathogenic mechanisms for impaired leukocyte mobility in pediatric patients having severe protein-calorie malnutrition; and pediatric aspects of diabetes mellitus.
- o Investigations on nutrition and cancer include research on: the biosynthesis of mammalian glycoproteins; lipids and membrane structures of leukemic leukocytes; asparagine biosynthesis in normal and tumor cells; hexosaminidase levels and diet; human mucosal structure and function; and normal and tumor cell regulation of folate polyglutamate synthesis.
- o In the areas of cardiovascular and lung disease, research includes: the regulation of cholesterol metabolism in cultured cells; coronary risk, family lifestyle and behavior change; outcomes of behavioral programs for chronic obstructive pulmonary disease and diabetes; the effects of diet on blood pressure; the effects of nutrition, age, and drugs on lung hyperoxia; preventive cardiology; and oxidants, stress and pulmonary prostaglandin metabolism.

The areas under study by the 78 recipients of the NIRA awards include metabolism in growth and development, fat metabolism and obesity, vitamin and trace mineral metabolism, immune function, eye disorders, trauma, hypertension and cardiovascular disease, and cancer. Studies in each of these areas are given below.

- o Studies on metabolism in growth and development include research on pregnancy and lactation, infant feeding, gastrointestinal development, neuroendocrine control, and total parenteral nutrition.



Research includes: effects of malnutrition on pregnancy or lactation; characterization and bioavailability of manganese binding molecules in human milk, cow's milk and infant formula; influence of differences in the protein/calorie ratio and energy intake on the rate and composition of growth of small premature infants; dietary and metabolic manipulations of lactose absorption in the intestine; the effects of qualitative and quantitative changes of dietary protein on the activity of the mucosal component of protein digestion in an animal model of pancreatic insufficiency; characterization of compositional and organizational changes in the microvillus membrane (MVM) of the gastrointestinal tract from suckling, weaning, and postweaned rats in terms of the qualitative (breast milk vs. artificial formula), quantitative (volume of milk ingested, duration of weaning period), and changes in nutrients provided during the perinatal period; the effects of postnatal diet, endocrine milieu, and increased bile acid pool on mediating the development of hepatic bile acid transport in the human infant; postnatal development of bile secretory, metabolic and structural functions of the liver; effect of nutrition on neonatal intestinal metabolism, specifically those factors controlling substrate oxidation in rat intestine during suckling, weaning, and postweaning periods; and effects of diet on attention span, activity level, anxiety, hyperactivity, aggression, and tantrums in 4-year-old children.

Studies include research on the evaluation of neuroendocrine control (i.e., the role of histamine) of drinking elicited by eating; the influence of feeding cycles on circadian body temperature rhythm in rats; neurological basis of taste-elicited ingestion and rejection of foods; and effects of foodstuffs such as carbohydrates and amino acids, on the functioning of neurons within the enteric nervous system of the cat; behavioral/observational assessments of food intake, physical activity, and parental influences on children's food intake and physical activity, as well as the relationship of these parameters to energy balance. Studies are also carried out on interactions of hormones, dietary fat, carbohydrates, and amino acids on leucine metabolism in the liver; and metabolism of dietary sulfur amino acids in altered liver function.

Research continues on the metabolic alterations induced by total parenteral nutrition in the rat; and intestinal membrane structure and functional development.

- o Research in the area of fat metabolism and obesity includes studies on the effect of energy intake on the rate and composition of weight gain in premature infants; effects of dietary intervention with food restriction on weight loss in obese (FA/FA) rats; and regulation of fat and protein synthesis.

Other studies include research on kinetics of lipolysis, i.e., the effect of diet on the roles of lipoprotein lipase and hepat-

ic lipase in the interconversion of triglyceride-rich lipoproteins in normal and hyperlipidemic plasma; the effect of weight loss and exercise on lipoprotein lipase; kinetic and biochemical modifications of lipoprotein lipase; regulation of cholesterol esterification in the intestine; and biliary tract motility in the fasting and fed state.

Other research includes studies on the role of beta endorphins on feeding and obesity; opioid peptides' effects on food intake, selection, and obesity; regulation of experimental obesity via the sympathetic adrenal axis; neurobehavioral analysis of glucagon on satiety; aerobic training and efficiency of energy utilization in animals; and contribution of energy yielding nutrients to hepatic fat accumulation.

- o Studies on vitamin and trace mineral metabolism include determination of the subcellular localization of vitamin A in mammalian epithelium tissues of the intestine, cornea, testis, and liver; characterization of B<sub>6</sub> dependency in I-mice, an inbred strain of mice that may serve as an animal model for a B<sub>6</sub> responsive genetic disease; the effects of changes in vitamin D metabolism during pregnancy on fetal growth and skeletal development; mechanisms and pathways of intestinal absorption of vitamin D sterols in rats, emphasizing factors influencing absorption that may be altered in gastrointestinal disease; and tocopherol status of patients with potentially compromised vitamin E status due to malnutrition and stress due to hyperoxia.

Other studies include research on the biological utilization of molybdenum; zinc nutrition and intestinal absorption of cholesterol, i.e., the intestinal absorption of dietary cholesterol, the chemical and physical characteristics of chylomicrons formed during active intestinal transport of cholesterol, and the metabolic turnover of chylomicron cholesterol as affected by the nutritional status of zinc; trace mineral bioavailability and metabolism studies; factors that influence the choline and methionine content in milk and tissue choline concentrations; and cellular mechanisms of chloride absorption and secretion by rabbit colon.

- o Studies on immune function include research on intestinal and hepatic defense mechanisms in immature animals using known hepatotoxins (proteases and endotoxins) prior to and following gavage feeding in breast-fed and bottle-fed animals; the effect of Schistosoma hematobium infection on nutritional status, i.e., anemia, growth, and physical fitness of school-age children in Kenya and the benefits of a safe and inexpensive oral drug on nutritional status; investigation of reduced host defense and nutritional status in the elderly determined by complete nutritional, hematological, and immunological assessments; effects of total parenteral nutrition systems and parenteral phospholipid infusions on cholesterol homeostasis in man; investigations on the effect of circulating IgG antibody on the uptake of enteric antigen in neonatal rabbits; and changes in

the morphology and metabolism of megakaryocytes and platelets in guinea pigs with cholesterol feeding and acute and chronic ethanol ingestion.

- o Studies on eye disorders include research on cytosol retinoid binding proteins (from the retina, pigment epithelium, testes, and liver of several species of animals) in order to understand their molecular structure, functions in the eye, and effect of deficiencies on altered retinol binding specificity and affinity; immunobiology of ocular surface Langerhans cells, i.e., changes in distribution, density, and membrane antigens/receptors of the cells in response to vitamin A deficiency; biochemical differences in the proteins, glycoproteins, and proteoglycans, and in the antiproteases in the eyes of vitamin A deficient animals that might account for the rapid corneal ulceration and stromal degradation that occurs in keratomalacia; corneal uptake and metabolism of topically applied retinoids with respect to their efficacy in the treatment of xerophthalmia and promotion of corneal wound healing; and the role of phosphorylation of the vitamin A pigment rhodopsin in vision and the role of calcium levels in regulating the phosphorylation process.

Other studies include research on the role of excitatory amino acids in the visual process vis-a-vis the photoreceptors and bipolar cell transmitters in the retina of fish, amphibians, and mammals; epidermal lipids and disorders of keratinization; and mechanisms that determine normal copper concentrations within intraocular compartments as well as those that cause an elevation in copper concentrations in intraocular fluids after an episode of uveitis.

- o Studies on hypertension and cardiovascular disease include measurement of cardiovascular parameters during maximal exercise (i.e., oxygen consumption, cardiac output, stroke volume, heart rate, and  $O_2$  extraction), as well as the measurement of pulmonary function, serum lipids, body composition, glucose tolerance, and echocardiographic left ventricular function in young (<25 years) and older (>50 years) athletes matched on the basis of training and performance; and alterations in the plasma lipoprotein profile, hepatic lipoprotein production, skeletal muscle and adipose tissue lipoprotein lipase activity, and vessel and tissue pathology as influenced by age, exercise, diet and hyperlipemia in individuals.

Other studies include the effect of exercise training on 60-year-old sedentary individuals in terms of  $O_2$  uptake, glucose tolerance, plasma insulin levels, and the development of coronary artery disease; effects of exercise and restricted feeding on the age-related physiological and biochemical changes in the mammalian heart with old age; and effectiveness, safety, and mechanism of the cholesterol-lowering effect of high glucose diets in normal subjects and patients with familial hypercholesterolemia (FH).

- o Studies on cancer include growth and differentiation of mast cells and T cells; sodium ions and mitogenic signaling; deoxyribonucleoside triphosphate metabolism; metabolism of N-13 ammonia and L-amino acids in murine tumors which are sensitive or resistant to glutaminase or asparaginase therapy; modulation of the development of normal granulocyte/monocyte colony forming cells by 12-O-tetradecanoylphorbol-13-acetate (TPA), retinoic acid, and prostaglandin E1; antitumorigenic effects of the pineal gland in nutritionally restricted rats; lymphocyte carcinogen metabolism in acute leukemia; receptors for reduced folates in human tissues important for the regulation of folate uptake and transport in normal cells as well as mutant cells; screening for dietary inhibitors of N-nitrosamine carcinogenesis; and relaxation training to reduce aversion to chemotherapy.
- o Studies on trauma include hypermetabolism after severe head injury in children; and intravenous lipid metabolism following burns.

#### THE INTRAMURAL RESEARCH PROGRAM

The total cost of the NIH intramural program in biomedical and behavioral nutrition research was \$13,096,000 for FY 1984 (see table I). Institutes supporting intramural research in nutrition include NCI, NHLBI, NIDR, NIADDK, NIAID, NICHD, NEI, and NIA. Most of this research takes place on the NIH campus in Bethesda; however, the NIA intramural program is located at the Gerontology Research Center in Baltimore, Maryland.

A major component of the intramural nutrition research program are the interagency reimbursement agreements of two Institutes (NIA and NCI) with the National Center for Health Statistics (NCHS) for the epidemiological followup of participants of the Health and Nutrition Examination Survey (NHANES I). This survey, conducted in 1971-74, collected dietary, biochemical, clinical, and anthropometric information on the nutritional status of a national sample of the U.S. population comprising 23,000 persons between the ages of 6 months and 74 years. The dietary data collected included calorie intake; calories as a proportion of RDA calories; nutrient density; protein, carbohydrate, and fat as a proportion of total calories; number of carbohydrate servings per day; proportion of carbohydrate servings from complex carbohydrate sources, and proportion of carbohydrate sources from individual food groups. The major emphasis of the followup survey is to relate the previously assessed dietary intake and biochemical test findings, chronic disease risk factors, environmental and occupational exposure, and the psychosocial characteristics of the population with morbidity and mortality occurring since the original survey.

The NIA study includes a cohort of 14,400 persons, who were between the ages of 25 and 74 years at the time of the original study, in



order to obtain specific information on dietary practices, alcohol use, exercise, smoking and changes in behavior over the past 10 years. Weight and blood pressure measurements are being made and related to previous measurements in order to assess changes in risk factors over time. The relationship between various nutritional factors and subsequent health status of the elderly is of particular interest in the hopes of improving the quality of life for all elderly persons.

NCI is utilizing the NHANES I data to examine regional differences in vitamin A and vitamin C intake, and fruit and vegetable intake in relation to the observed North-South gradient in colon, rectal, and breast cancer mortality. The intake of vitamin A, retinol, carotene, and vitamin C (based on 24-hour recalls); the intake of vitamins A and C (based on food frequencies); the frequency of fruit and vegetable consumption; and serum vitamin A levels are being compared. Using 24-hour dietary recall data, individual foods are being ranked by their contribution to total vitamin A intake for various age-sex-race region subpopulations. This information is being used in developing dietary interviews that will assess vitamin A intake and its relationship to cancer risk. In addition, the possible relationships between vitamin intake, biochemical and other indices of nutritional status, and subsequent health status including trends in potential risk factors for cancer will be examined over time.

Also, NCI is examining the possible effects of various factors (including diet, age, sex, race, poverty status, pregnancy-lactation status, region of inhabitancy, and individual variation) on serum vitamin A levels in a national sample of 14,000 adults from NHANES I. The serum vitamin A levels are of interest since some prospective studies have shown that mean serum vitamin A levels are lower among those persons who develop cancer. A specific hypothesis being tested is whether serum vitamin A levels are significantly affected by vitamin A intake within a well-fed population such as the U.S.

Another component of NCI's research evaluates the NHANES I dietary and anthropometric data from 100 women between the ages of 12 and 18 years as predictors of age at menarche and in relation to the development of breast cancer.

Other NCI studies under way examine the relationship between nutrition and cancer etiology through basic research at the molecular level, particularly of cancer chemoprevention with vitamin A and its analogs. Dietary habits and nutrient consumption of selected cohort populations are being analyzed in relation to the incidence of different cancers, with investigations under way on general nutritional status, anthropometric and biochemical indices, as well as cooking practices. Another research priority is the assessment of the efficacy of total parenteral nutrition (TPN) for the support of the cancer patient.

Studies of vitamin A and its synthetic analogs, the retinoids, have shown that supplementation with retinoids can reverse tissue metaplasia and neoplasia in various laboratory models through the resto-



ration of normal cell differentiation, and when given to animals can prevent chemical and viral induced carcinogenesis. Phase I studies are now under way to examine three new oral synthetic retinoids in terms of their basic pharmacokinetics, recommended doses, maximum doses, and drug toxicity. The maximum duration of continuous treatment will be 6 months. These drugs are also being tested for their possible therapeutic use for the dermatological conditions of acne, psoriasis, disorders of keratinization (ichthyoses and Darier's disease), basal cell carcinoma, and other related dermatological disorders, as well as to establish safe and tolerated doses for Phase II-III chemoprevention trials.

Skin cancer chemoprevention through the use of vitamin A involves extensive research on the morphological effects, biochemical mechanisms, metabolic pathways, and dose-toxicity of synthetic vitamin A (13-cis-retinoic acid) and its analogs in cell cultures and laboratory animals. Also, a 5-year randomized double-blind clinical trial of 1,800 subjects at 10 participating centers is currently examining the effectiveness of low doses (10 mg/day) of isotretinoin in reducing the incidence of basal cell carcinomas in a high risk population and the possible side effects associated with the long-term administration of such low doses. Case reports have shown that isotretinoin can prevent the appearance of new basal cell carcinomas for 4 years in patients at high risk of developing new tumors. Such research has provided important information on the cellular and molecular basis of skin carcinogenesis as well as the therapeutic value and antipromoting properties of vitamin A, both before and after the onset of malignancy.

Basic studies on the effects of retinoids on tumor cell growth have shown that in the presence of retinol or retinoic acid, spontaneously transformed mouse fibroblasts (BALB/c-3T 12-3 cells) stop growing at a lower saturation density (approximately 120,000 cells/cm<sup>2</sup>). Retinoid treatment also enhanced the adhesion of cells to the culture vessel surface and to each other. Other studies on the biochemical actions of vitamin A analyze the subcellular fractions of rat liver for the topical distribution of mannosyl transferase that glycosylates the lipid intermediate retinyl phosphate and the polyisoprenoid derivative dolichyl phosphate. In vitamin A deficiency, the liver pools of retinyl palmitate and retinyl phosphate are depleted, however, dolichyl phosphate levels increased fourfold. This same depletion of retinyl palmitate and retinyl phosphate occur in transplanted as well as primary rat hepatoma tissue. The vitamin A depletion of the tumor tissue is thought to be either the consequence of cell selection during carcinogenesis or a permissive condition for the development of tumor from initiated cells.

Other studies are investigating the alteration of carcinogenesis in the liver by the dietary lipotropes choline, methionine, folic acid, and vitamin B<sub>12</sub>. The hypothesis that physiological methyl deficiency promotes hepatocarcinogenesis is being tested by determining the carcinogenic and liver tumor promotion activities of methyl deficient diets, and the effects of dietary methyl donors on the tumorigenic activities of epigenetic carcinogens and tumor promoters. The study

attempts to establish the relationship between methyl insufficiency and the promotion of liver cancer as a result of the hypomethylation of DNA.

Studies of the murine L1210 leukemia cells which are resistant to L-phenylalanine mustard (L-PAM) have shown that these cells can be sensitized to L-PAM in vitro and in vivo by reducing the cellular concentration of glutathione either through pharmacological or nutritional means. The in vivo reduction of glutathione in the tumor cell through nutrition is accomplished by the use of defined amino acid diets devoid of L-cystine and with a reduction of L-methionine.

Experimental systems have also been established for assessing the effects of fatty acids on the growth of normal cells as well as on carcinogen-induced mammary tumors in rats. Studies have shown that all of the unsaturated fatty acids present in the mammary glands in appreciable amounts promote cell growth. Oleic acid appears to promote the maximum growth rate of tumor cells, while linoleic or linolenic acid promote maximum growth of normal cells. Both normal and tumor cells are inhibited by saturated fatty acids.

Some studies have shown that exogenous insulin administered to sarcoma-bearing rats increases spontaneous food intake, nitrogen balance, and gain in body weight, but decreases muscle catabolism (3-methylhistidine) without stimulating tumor growth. The animals treated with insulin do not have a longer survival, but do have a greater carcass mass and accrual of both protein and fat similar to that of normal body composition. Exogenous insulin appears to preserve the host without feeding the tumor.

The physiological basis for cancer cachexia is also under investigation with physiological and behavioral control of food and water intake being measured in normal and cancerous animals. An in vitro assay for protein synthesis and breakdown has been developed by incubating weanling rats' extremity muscles in a physiological buffer system. Test sera from normal, cachectic, and septic animals are added to the system in order to determine whether a circulating factor is present in the sera that decreases protein synthesis and increases protein catabolism. In addition, an in vivo assay used to determine the cachectic factor involves the administration of sera from cancer-bearing animals that are not eating to normal animals and then measuring food intake. If such a factor does appear from these assays, investigators will attempt to determine whether it is a tumor-derived factor or a host-derived factor responding to the tumor and then to biochemically characterize the factor.

Cancer cachexia and malnutrition of the host can impair physical defense barriers and may also impede granulocyte recovery. Studies are under way to determine the influence of variations in protein/carbohydrate intake on cyclophosphamide (CP) induced myelosuppression. The aim of these studies is to develop methods that define patients at high risk for infection and to improve the ability to diagnose infections early, treat them effectively, and ultimately prevent them.

Animal studies as well as epidemiological studies have been used to assess the role of specific dietary factors in cancer prevention. Information on such agents appears to be lacking in terms of their quality and form in the food supply, bioavailability, biochemical effects, and interactions with other nutrients. In cooperation with the Beltsville Human Nutrition Research Center, the Division of Cancer Prevention and Control is developing the analytical methods for the routine analysis of nutrients and investigating the pharmacodynamics and interactions of dietary factors identified as possible cancer preventive agents.

Selenium is one dietary factor considered as possibly important for the prevention of cancer and therefore is being analyzed for its pharmacokinetics and bioavailability. The initial phase of the selenium studies examines the pharmacokinetics of a single dose of sodium selenite (inorganic form) and selenomethionine (organic form) in a healthy population having an adequate baseline selenium intake. The parameters measured include percent absorption, maximum concentration, and half-life for single doses in both fasting and nonfasting individuals. In addition, the bioavailability and health effects of multiple doses of inorganic and organic selenium will be examined and compared in terms of their absorption, distribution, and excretion. Other studies will correlate the dietary intake of beta-carotene with beta-carotene, retinol and retinol binding proteins in the blood as well as the interaction of dietary fat and fiber intake on mineral and vitamin metabolism.

Two additional efforts of DCPC under way to ensure the standardization of data on selected variables associated with the incidence of cancer are the development of a core questionnaire that will collect a common data base on smoking, diet, and occupation and psychosocial variables; and a dietary assessment questionnaire used as part of the core questionnaire for use in a large clinical trial as well as determining individual dietary intakes. Another study assesses whether it is possible to gather accurate information about an individual's past dietary intake. These instruments which allow for the collection of baseline data in an identical manner will help to improve the interpretation of results from different studies, facilitate the resolution of conflicting data, and enhance the comparability of results from the different clinical trials that address the issues of nutrition and cancer.

Several case control and cross cultural surveys are under way to study the incidence of cancers of the colon, breast, esophagus, lung, pancreas, and stomach in relation to dietary patterns of specific populations, biochemical and anthropometric indices, and general nutritional status. Case control studies have been initiated in high risk areas with unusually high mortality rates from cancer. For example, three studies are being carried out in Finland: One 5-year study examines the possible chemopreventive effects of a daily beta-carotene supplement of 15 mg given to cigarette smokers on the incidence of lung cancer. The second, a case control study on breast cancer, investigates the relationship of serum levels and dietary intake of selenium, vitamins A, E, and C, fats, and other nutrients



on the incidence of breast cancer in individuals with benign breast disease. The third study examines the associations between various dietary components and different cancers using dietary history information that was previously collected from a subgroup of the population that developed cancer.

In order to assess the efficacy of TPN as a means of nutritional support for the cancer bearing host, prospective randomized studies of TPN as an adjunct to aggressive chemotherapy and radiation treatment are under way. Cancer patients receiving TPN are examined for deficiencies in vitamins, trace metals (zinc, copper, and chromium), and essential fatty acids, as well as for changes in gluconeogenesis, protein synthesis, glucose disposal, body composition for potassium, alanine kinetics, mineral balance, and requirements for all known nutrients.

Also within the intramural program, the Office of Cancer Communications has begun its Cancer Prevention Awareness Program which is providing messages to the public that proclaim that changes in dietary habits (e.g., increasing fiber, reducing fat intake) can reduce an individual's risk of cancer.

NHLBI has several intramural investigations that attempt to clarify the structure, biosynthesis, transport and metabolism of lipoproteins since their moieties (i.e., cholesterol esters, triglycerides, and apoproteins) are significant in the development of atherosclerosis and coronary heart disease. The apolipoprotein composition of plasma lipoproteins is considered as the governing factor in directing lipoprotein metabolism. Knowledge of the stoichiometry and equilibrium constants for the specific apolipoprotein complexes (A-I, A-II, C-I, C-III, E, and H) formed in the plasma has provided a framework for evaluating the rate that apolipoproteins control lipid metabolism, e.g. cholesterol and triglyceride transport. It has been shown that apolipoprotein E (apo E) is important in modulating the catabolism of triglyceride-rich lipoproteins, and that apo E-II, an abnormal form of apo E, is associated with type III hyperlipoproteinemia and is associated with decreased concentrations of low density lipoproteins (LDL). Individuals with apo E-II experience elevations in triglycerides after a high fat meal along with an increased production of apo E.

Other conditions resulting from abnormal apolipoprotein metabolism are Tangier disease and familial hypercholesterolemia. Individuals with Tangier disease have an abnormal apo A-I that is catabolized more rapidly than in normal individuals. This causes low HDL concentrations in the blood. Patients with familial hypercholesterolemia (FH) have decreased plasma concentrations of apo A-I and increased concentrations of apo E. The LDL receptor activity in these patients is highly correlated with plasma cholesterol levels, severity of clinical disease, and response to treatment. Determination of apolipoprotein levels in patients with premature coronary artery disease showed that levels of apolipoprotein A-I and C-II, rather than plasma cholesterol and triglyceride levels, were more clearly identified within this atherosclerotic population. In order to further examine

the apolipoproteins found in various dyslipoproteinemic individuals, a new two-dimensional electrophoretic technique is being used to determine apolipoprotein concentrations, molecular weight, and apolipoprotein variants.

Other studies are under way to examine the pathophysiology of the dyslipidemias and to increase our understanding of normal lipoprotein physiology. These include investigation of the effects of the different lipoproteins and apolipoproteins on lipid metabolism of various cell types (i.e., fibroblasts, macrophages, and hepatocytes) in normal as well as dyslipidemic individuals. Cellular metabolism has been investigated in persons with FH, abetalipoproteinemia, Wolman's disease, cholesteryl ester storage disease, Tangier disease, and Erdheim-Chester disease. The adult human liver appears to have specific receptor or recognition sites for apo A-I, E, and B. Analysis of these hepatic receptors in several dyslipidemic states has shown specific genetic and physiological control of the receptors.

In addition to lipoprotein and apoprotein, per se, investigators are also quantitatively evaluating the molecular properties of lipoprotein lipase and hepatic lipase, two enzymes responsible for triglyceride hydrolysis. The activity of both enzymes will be studied in normals as well as in individuals with disorders of lipid metabolism, and correlated with lipid and apolipoprotein concentrations in the blood.

Research also continues on the control of blood pressure by restriction of dietary sodium intake and the activity of the sympathetic nervous system. Individuals with essential hypertension can be categorized as salt-sensitive or non-salt-sensitive depending on whether blood pressure increases or remains the same when sodium intake is increased from 9 to 249 mEq/day. Normally, when sodium intake is increased, sympathetic activity is decreased and the dopaminergic nervous system, a mediator of the body's natriuretic response, is stimulated. The sympathetic nervous system is thought to be an etiologic factor in essential hypertension, while the role of the dopaminergic system is unclear. In one study, salt-sensitive patients did not show the suppression of sympathetic activity with decreases in plasma and urinary norepinephrine levels that normally occur when a low sodium intake is changed to a high sodium intake. Thus, the persistence of increased sympathetic activity in these individuals might reflect impaired sodium excretion that caused the increase in blood pressure. In non-salt-sensitive individuals with essential hypertension, the plasma and urinary norepinephrine decreased during high salt intake and urinary dopamine increased. Thus, the increased dopaminergic activity may be a factor in the development of hypertension in the non-salt-sensitive individuals.

Another study of male Sprague-Dawley rats is measuring the impact of excess dietary salt on sodium homeostasis of the thymocyte cell. Both intracellular sodium content and  $^{22}\text{Na}$  efflux are being measured. Research will continue to investigate the possible mechanisms, such as sodium pump inhibitors, related to the regulation of blood pressure.



Studies under way as part of NIDR's intramural program examine the effects of sugar substitutes on growth, acid production, and glucose synthesis by Streptococcus mutans in the mouth. Data have shown that the sucrose derivatives palatinose and palatinin did not support growth or acid formation by several different species of oral streptococci, that these compounds inhibited glucan formation by S. mutans, and that xylitol also inhibited growth and acid production by S. mutans, S. sanguis, S. mitior and A. viscosus. Another non-sucrose sweetener--acesulfam K--which is 300-350 times sweeter than sucrose was also investigated in terms of caries development in rats and found to be noncariogenic.

Because plaque pH is known to affect caries development, a device is being tested that would measure the pH of intraoral plaque when challenged with different foods. A fluoride releasing device is also being investigated in rats for its anticaries effects. Data indicate that the marked reduction of caries produced by the device was due to the topical effects of fluoride. The effectiveness of fluoride mouthrinses and tablets given to school children beginning in kindergarten and first grade and continued for 8 and 9 years is being studied in terms of reducing the incidence of caries. Other studies investigate the anomalies in taste perceptions with procedures that quantify not only taste detection thresholds but also the intensity and pleasantness of various taste stimuli when provided at commonly encountered intensity levels.

NIADCK conducts nutritional studies that attempt to determine the metabolic roles of various nutrients in the body and the effects of different levels of nutrient intake on metabolism and physiological function. For example, studies are being done to determine if rats on different diets produce multiple types of very low density lipoproteins (VLDL) which differ in their apc B components. Other studies examine the transport of fatty acids between capillary lumen and the interior of parenchymal cells. Data support the concept that lipolytic products travel in the outer leaflets of cell membranes and that they can form lamellar extensions of the leaflets under certain conditions. In addition, studies that have purified lingual (pharyngeal) lipase have shown that bile salts--particularly sodium taurodeoxycholate--and calcium ions together greatly enhance the action of lingual lipase on the metabolism of long chain triacylglycerol. Findings from this research indicate that lingual lipase can act on dietary fat in the small intestine and thereby could be helpful in cases of pancreatic insufficiency.

Many studies are investigating the action of insulin in the regulation of glucose transport and metabolism. Some preliminary evidence suggests that insulin's stimulatory action on glucose transport in isolated rat adipose cells occurs through a subcellular redistribution of glucose transporters rapidly cycling in an exocytic/endocytic-like fashion; insulin acts at a step whereby glucose transporters associated with the plasma membrane become functional, and cAMP-mediated counter-regulation of insulin-stimulated glucose transport by catecholamines comprises both the regulation of the subcellu-

lar distribution of glucose transporters and the modulation of the activity of those glucose transporters present in the plasma membrane. Insulin also appears to stimulate glucose transport in isolated guinea pigs and human adipose cells and rat diaphragm through this same translocation mechanism. Basic research investigations under way have also shown that the adipocytes of guinea pigs are insulin resistant due to a reduced number of glucose carrier proteins.

Studies have also examined the effects of overnutrition on the development of insulin resistance in subjects with normal glucose tolerance. The results thus far indicate that acute overnutrition does play a role in the development of insulin resistance, and that changes in glucose disposal rates are related to in vivo measurements of non-oxidative glucose disposal rates as determined by indirect calorimetry.

Other studies have suggested that muscle glycogen depletion following exercise in animals is associated with increased insulin sensitivity. Studies in man have shown that after exercise, muscle glycogen decreases significantly while muscle glycogen synthase activity increases significantly, basal and insulin stimulated carbohydrate oxidation rates decrease, and carbohydrate storage rates increase. These results suggest that muscle glycogen synthase activity may be rate limiting for carbohydrate storage rates and therefore for total glucose disposal rates in glycogen depleted men.

Studies continue to attempt to learn more about the mechanisms of action for various hormones and enzymes necessary for metabolism. Gastrin, secretin, cholecystokinin, and bombesin are being studied through in vitro systems while the action of dihydrofolate reductase and its unique molecular biology are being examined in various animal studies.

Clinical research is under way to examine the relationship of nutritional factors to the etiology, morbidity and mortality of metabolic and other diseases or conditions, such as diabetes mellitus, periodontal disease, cystic fibrosis, obesity, hypochloremic metabolic alkalosis, and cystinosis. Clinical studies of the Pima Indians have shown them to have the highest known prevalence and incidence of noninsulin-dependent diabetes mellitus in the world. They also have a high prevalence of obesity, low plasma cholesterol levels, reduced low density lipoprotein (LDL) synthesis, and a decreased incidence of cardiovascular disease. This population appears to be insulin resistant as well as hyperinsulinemic; the hyperinsulinemia found in Pima children is thought to contribute to the development of obesity and diabetes in adulthood. Recently, a study to examine the possible relationship of periodontal and other oral diseases to diabetes in this population has begun. Lipoprotein metabolism in Pima Indians is being investigated in order to further understand the control of lipoprotein metabolism and how lipid metabolism is influenced by obesity and diabetes. Preliminary studies have shown that a large proportion of VLDL is metabolized without conversion to LDL and therefore this alternate pathway might be a mechanism for maintenance of the low LDL levels in this population. Obesity was

also associated with an increased flux of free fatty acids without increasing plasma concentrations, which could account for increased VLDL production in these individuals. Total plasma cholesterol and VLDL levels increased with increasing obesity whereas high density lipoprotein (HDL) cholesterol decreased.

It has also been proposed that the high incidence of obesity in the Pima Indians may be due to a thrifty gene, one that would predispose them to store energy more efficiently. It appears that in the obese Pimas, although their basal plasma concentrations of norepinephrine is similar to that of Caucasians, plasma levels are higher following norepinephrine infusions. Thus, they appear to suffer from a clearance defect for norepinephrine as well as a decreased thermogenic response to the hormone following overfeeding. The studies suggest a large flux of substrates and regulators (i.e., insulin) which causes the overproduction of lipoproteins; however, compensatory mechanisms are operative that result in the maintenance of low plasma concentrations.

Two South Pacific populations--the Polynesians of Rarotonga and Melanesians of New Hebrides--are also being studied in terms of differences in lipoprotein metabolism. Data indicate that cholesterol and triglyceride levels in the Rarotongas were higher than those in the Melanesians, and that the Rarotongas have a higher incidence of cardiovascular disease.

In clinical studies of cystic fibrosis (CF), attempts are being made to define more precisely the abnormalities that contribute to the pulmonary and gastrointestinal symptoms of this disease. Lingual lipase activity is being studied in order to further clarify its role in fat absorption in these patients, while serum amylase and its isoenzymes are also being analyzed for diagnostic purposes. The altered fatty acid composition found in the blood and tissue lipids of patients with CF is more often found in those patients with malabsorption problems than in those with normal pancreatic function. Recent studies suggest that the lower caloric intake of the CF patient relative to their caloric requirement may lead to an increased utilization of absorbed essential fatty acids (i.e., linoleic acid).

From studies on the pathogenesis of cystinosis, an inherited disorder characterized by excessive intralysosomal accumulations of the amino acid cystine, it appears that the disorder is due to a defective carrier mechanism required for the escape of L-cystine from the intralysosomal space; this explains the large accumulation of cystine found in this disease.

The evaluation of hypersensitivity reactions after the ingestion of foods continues to be an important research area supported by NIAID. The clinical management of food hypersensitivity (allergy) is complicated by the need for extensive differential diagnosis, the absence of definitive diagnostic procedures, and the lack of satisfactory prophylactic therapy. In general, the approach to the management of food allergy is the same as the approach to the management of allergic diseases of the skin and of the upper and lower respiratory



tracts: identification of the offending agent and the treatment of adverse reactions. Results from one study of 45 patients with a history of immediate adverse reactions to foods showed that the majority of the reactions involved the gastrointestinal tract alone or in combination with the skin or respiratory tract, and that the foods most frequently involved were shellfish, peanuts, eggs, fish, tomatoes, and walnuts. The data suggest that an immediate adverse reaction to food may initially present itself in adulthood. These individuals tend to be atopic, usually three or fewer foods are implicated, and sensitivities may persist for years.

Investigations are also under way on the effects of other agents, such as sulfites added to foods as preservatives, on severe asthmatics and individuals with recurrent idiopathic anaphylaxis and systemic mastocytosis. Preliminary data on patients with these diseases who are given increasing amounts of the sulfites suggest that the majority of patients with idiopathic anaphylaxis and systemic mastocytosis are not sensitive to sulfites. However, a subset of severe asthmatics do react adversely to sulfites with increased difficulty in breathing.

Studies carried out as part of the NICHD intramural nutrition program range from research on molecular genetics, inborn errors of metabolism, and endocrinological and reproductive research, to epidemiological research on breast versus bottle feeding. Studies on genetic expression with nutritional deficiencies have shown that with a nutrient imbalance, guanosine 3,5'-bipyrophosphate (ppGpp) is involved in the expression of approximately one-half of the E. coli genes, but has no regulatory effects during normal growth. Lethal consequences of the rel S mutation, which abolished ppGpp accumulation during energy starvation, have been observed. The rel A and rel S double mutant is markedly defective in its ability to curtail cellular functions when adapting from luxuriant growth to nutritional impoverishment.

Research continues on various inborn errors of metabolism, including cystinosis, glutathione synthase deficiency, glutathionuria, gamma glutamylcysteine synthase deficiency, homocystinuria, glucose-6-phosphate dehydrogenase deficiency, phenylketonuria, galactosemia, and adrenal leukodystrophy; investigators are particularly interested in developing nutritional therapy and new diagnostic techniques in these conditions. The etiology of cystinosis has been discovered and the first transmembrane lysosomal transport system for amino acids has been identified. The investigator plans to determine which small molecules are carried across the lysosomal membrane and what is the basic defect in lysosomal diseases that involve the storage of free compounds. Currently, treatments of such diseases that are being investigated include using pantethine for cystinosis, betaine for homocystinuria, and cysteamine for type III hyperlipidemia. A clinical trial is examining the safety and efficacy of cysteamine for the treatment of children with nephropathic cystinosis, a metabolic disease that leads to end-stage renal disease before 10 years of age. Cysteamine's effectiveness will be evaluated by determining the creatinine clearance values of the treated children.

The study of obesity in children with Prader-Willi syndrome attempts to detect the anatomic and physiological causes for the lack of the sense of satiety, to establish whether the mechanism involved is the same as in patients with exogenous obesity, to identify any special biochemical or physiological features in these patients, and to determine the pattern of absorption and metabolism of carbohydrates in Prader-Willi patients and those children with exogenous obesity.

Children being treated for glycogen storage disease (GSD) have shown significant improvements in maintaining normal blood glucose levels with the administration of corn starch every 6 hours. These studies also investigate the possible therapeutic effects of glucose, polycose, rice starch, potato starch, cooked corn, cooked potato and cooked rice containing equivalent amounts of complex carbohydrates in maintaining normal blood glucose levels in these patients. The usefulness of starch administration in mollifying and preventing the myopathy of Type III GSD is also being examined.

The use of magnesium in infants with apnea and bradycardia is being investigated since animals deficient in magnesium often develop these symptoms. Magnesium deficiency in animals appears also to manifest itself with retention of magnesium by the kidney. Since rat dams fed 150 mg of magnesium ( $\text{MgCO}_3$ ) appear to suffer high fetal wastage, investigators are looking into the effects of feeding dolomite [ $\text{CaMg}(\text{CO}_3)_2$ ] in these animals. Investigators also are examining the effects of prolonged furosemide administration on magnesium metabolism; changes of bone magnesium and calcium in very young nursing rats with congenital magnesium deficiency; histopathological changes in the lungs of rats with acute magnesium deficiency using light and electron microscopy; the distribution of neurotransmitters by fluorescence microscopy studies; the pathogenesis of the shock-like episode of magnesium deficiency through studies of neurotransmitters release; and differences between congenital and acquired magnesium deficiency in young animals.

Other studies examine the trace elements of sodium and calcium, as well as the use of vitamin supplements. These studies look at the physiological and pathological aspects of the renin angiotensin system with emphasis on the regulation of aldosterone secretion. Specific issues include the regulation of adrenal sensitivity to angiotensin II during altered sodium intake and the mechanisms of steroidogenesis in the adrenal glomerulosa cell. Changes in the kinetics of calcium metabolism in normal children at various stages of growth from infancy to puberty are also under investigation. Another study is examining whether there is a link between vitamin supplements taken in the periconceptual period and the risk of neural tube defects in the infant.

Research on the effects of ethanol on the mother and fetus and on the possible manifestation of fetal alcohol syndrome (FAS) is an important area of nutrition research. Studies that are under way attempt to identify and characterize the biochemical markers in children that may predispose them to alcoholism and/or alcohol-induced dement-



tia in adulthood; to explore the biochemical mechanisms of fetal alcohol syndrome; to develop new methods to treat borderline FAS children in order to improve their postnatal growth and central nervous system retardation; to delineate the effects of a thiamine deficient diet and ethanol on fetal development using an animal model; and to determine the effects of ethanol on various neuropeptides.

Investigators have also shown that changes in thyroid hormones during hypocaloric feeding in humans can now be demonstrated with the use of the pulse wave arrival time (QKd). Data have shown that with prolonged hypocaloric feeding, the QKd is prolonged, and therefore, suggests hypothyroidism at the target organ level. Oral supplementation with  $T_3$  rather than  $T_4$  prevents these changes in QKd. Changes observed in peripheral thyroid hormone levels during hypocaloric feeding appear to be due to adaptive mechanisms that result in hypometabolism.

Results from the study on trends in breast and bottle feeding in Pima women of the Gila River reservation have shown that parity had a positive association with bottle feeding. The highest proportion of bottle feeders occurred among women with small families before 1963 and with large families after 1963. Prenatal and postnatal care had a limited influence on the determinants of breast and bottle feeding. The study shows that mother and infant-oriented reasons dominated in the selection of breast or bottle feeding the first infant; while work-related reasons had a stronger influence on the decisionmaking process for feeding the last child. This study will now determine whether breast feeding or bottle feeding is associated with reduced infections in children.

Another study of 1,275 American mothers, 800 of whom are breast feeders and 475 are bottle feeders, includes examination of independent and joint effects of various factors on the frequency and duration of breast and bottle feeding. These factors include prenatal and postnatal medical services; the mother's perception of support from peers, family and medical environments; confidence, enthusiasm and attitude of the mother toward breast feeding; sociodemographic factors; physiological conditions; and the initial feeding pattern, as well as changes over time.

NEI investigators are examining associations between specific nutrients and normal ocular health and function, as well as various ocular diseases. A new intracellular binding protein for retinoids has been identified in the subretinal space; research continues to elucidate the protein's role in ocular vitamin A metabolism and document its appearance at progressive stages of embryonic and newborn development.

Concentrations of vitamins A and E in the pigmented rat retina and retinal pigment epithelium are known to affect the formation and accumulation of lipofuscin pigment. It was found that the amount of lipofuscin in the retinal pigment epithelium is a linear function of the logarithm of dietary vitamin A levels whereas vitamin E

deficiency accelerates the accumulation of lipofuscin in RPE, which is identical to the pigment that accumulates with aging. Vitamin A deficiency in rats results in a striking decrease in the amounts of lipofuscin that accumulates in RPE as a result of normal aging or vitamin E deficiency. Scientists are also studying independent changes in lipofuscin associated only with the aging process.

Investigators examine the distribution of calcium, copper and zinc concentrations in the retina, pigmented epithelium, choroid, and biological fluids in animal models of human retinal degeneration and in human retinal diseases. The effects of nutrition and genetic background on the progress of chorioretinal degeneration in the retinal dystrophic pigmented RCS rat are under investigation as well as the etiologies of cataracts and gyrate atrophy. The various etiologies of cataracts being examined include: the distribution of inorganic elements such as copper, zinc, selenium, and calcium in cataracts associated with retinal degeneration; the role of exogenous or endogenous oxidative stress in the formation of cataracts; and changes in the composition and metabolism of lipids in the plasma membranes and lenses. Inhibitors to the formation of cataracts through the limitation of aldose reductase activity are also being explored. The potential role of aldose reductase and pyrroline-5-carboxylate reductase in cataractogenesis is being investigated. The latter enzyme is involved in the metabolic conversion of ornithine and glutamine to proline, and therefore, may regulate the cellular redox potentials and increase ATP levels through the pentose shunt. Studies of gyrate atrophy attempt to determine how dietary manipulations of pyridoxine administration modify ornithine levels and, in fact, arrest or improve conditions associated with the disease. A study of senile macular degeneration investigates whether the administration of vitamin E and vitamin C protects against vision loss in the good eye of persons suffering from senile macular degeneration in the other eye.

Nutrition as it relates to the aging process is being studied by NIA's intramural scientists in both animal models and human subjects. One area of interest is the mechanism(s) by which undernutrition affects various physiological functions with aging. In one study of male Wistar rats subjected to dietary restriction by alternate days of feeding and fasting, the normal age-associated loss of striatal dopamine receptors in the brain was substantially retarded. For example, the dopamine receptor concentrations in the striata of 24-month-old rats that had been on the restricted diet since weaning were 50 percent greater than those of the control animals of the same age given free access to food. Data collected on the rate of activity of specific enzymes with age support the concept that the rate of aging of most biochemical variables is decreased in those animals with dietary restrictions. However, dietary restriction did not significantly increase the life span of the animals. In fact, in animals aged 17 to 19.5 months a diet providing 50 percent of the RDA for vitamins decreased their life expectancy. Longevity in these animals therefore may be increased by ensuring the ingestion of the RDA for vitamins daily.

Dietary restriction is also being studied in experiments using the monkey Macaca mulatta, in terms of its effects on age-related behavioral changes such as motor performance, thermoregulation, learning, and memory.

Another study is examining the relationship of age to the biological responsiveness of hormones and hormone sensitive tissues. Age-related alterations of beta-adrenergic mediated lipolysis in the rat indicate that the amount and type of fat in the diet affect the hormone sensitive lipolytic response. Dietary fat was shown to have a profound effect on the lipid composition of cell membranes, which in turn controls the activity of numerous cell membrane enzymes including the hormone sensitive adenylate cyclase system.

Dietary fat, however, does not affect every tissue in the same way within the same animal, e.g., a diet high in unsaturated fat has little or no effect on fat cell membranes but greatly affects liver cells, which exhibit an increased hormone responsiveness to both catecholamines (epinephrine) and the polypeptide hormones (glucagon). In addition, a high fat diet inhibits to a large degree lipolytic responsiveness. The control of lipolysis with age is a complex area of nutrition research and will require further research on the inter-relationships of diet and aging.

An important aspect of the NIA intramural program involves human studies under way as part of the Baltimore Longitudinal Study of Aging (BLSA), initiated in 1958 to observe the same subjects over a long period of time in order to quantify true age changes and elucidate the mechanisms underlying these changes. The study group includes 1,000 male and female subjects, ranging from 20 to 96 years of age, who return every 2 years for reevaluation and are enrolled in the study for life. Cohorts from this study population are being examined for changes in bone and skeleton, oral health status, salivary gland function, taste thresholds, plasma lipids, and nutrient intake.

Osteoarthritis, a degenerative joint disease, and bone loss are the two principal age-related changes to the human skeleton. Advanced cases of the former produce severe restrictions of movement associated with pain, while advanced bone loss is likely to result in osteoporosis and frequent bone fractures. Dietary, genetic, and epidemiological factors are being examined in terms of their effects on three skeletal sites--hand-wrist, ulna and radius, and vertebral column--of three different populations, i.e., the participants of the Baltimore Longitudinal Study, a sample of Guamanians (Chamorros), and among patients afflicted with amyotrophic lateral sclerosis/parkinsonism dementia complex of Guam.

Demographic, socioeconomic and dental characteristics are being determined in 254 BLSA participants, who will serve as a basic study population for future cross-sectional and longitudinal investigations of aging and oral health status and function. One study of salivary gland function in BLSA subjects has shown a linear decrease in sodium secretion into the stimulated parotid salivary gland function with age. Males showed a greater decrease than females.



Studies on quality-specific variation in taste thresholds with aging include the detection of taste thresholds for the four basic taste qualities in 81 adults between 23 and 88 years of age. Data indicate that sodium chloride thresholds have a small but significant increase with age; quinine sulfate thresholds have a similar increase but are less significantly related to age; sucrose and citric acid thresholds are not significantly related to age; and citric acid thresholds appear to be different in males and females. Thus, the detection thresholds for the four taste qualities undergo different changes with age.

An analysis of plasma cholesterol values in BLSA participants show that levels increase in early adult life and decrease in late life. All age cohorts showed a significant decline in plasma cholesterol levels between the 1950's and 1970's. The change in body weight, polyunsaturated/saturated fatty acid ratio in the diet, and dietary cholesterol explains only a small percentage of this secular effect.

In order to gain insight on the nutrient intake across the adult age span, 180 BLSA male participants recorded 7-day dietary diaries during three time periods: 1961 to 1965, 1966 to 1970, and 1971 to 1975. At the time of the first dietary diary, their ages ranged from 35 to 74 years. The analysis of the effects of aging, cohort, and time on diet utilized three research designs concurrently--cross-sectional, longitudinal, and time series. The nutrients considered were calories, protein, carbohydrate, fat, saturated fatty acids, polyunsaturated fatty acids, and cholesterol. The data indicate that the intake of calories, fat, saturated fatty acids, and cholesterol decrease with age, while polyunsaturated fatty acid intake increased. Cohort effects were not observed for any of the nutrients.

The Division of Research Services (DRS) provides support to the intramural research efforts of the NIH. Included in these services is a program in laboratory animal nutrition that routinely provides investigators with assistance in matters relating to animal diets. This assistance ranges from providing information regarding the nutrient concentrations of specific diets to direct collaboration in studies where dietary nutrients is the major variable and the formulation of special experimental diets is required. The staff of this program is also involved in monitoring the quality of animal diets purchased for use throughout the NIH. This is accomplished by routinely analyzing diet samples for various nutrient and potential contaminant concentrations.

The laboratory animal nutrition program is responsible for conducting research with the objective of improving the nutritional status of animal species used in research and thus improve the overall quality of animal models. This research has resulted in the development of an open formula diet for each of the animal species used in significant numbers in biomedical research. These open formula diets are not only being used at NIH but also throughout the biomedical research community as standard reference diets. Since the ingredient composition of open formula diets are readily available, the formula-

tions can be altered to produce diets with either deficient or excess nutrient concentrations for programs requiring animal models to study nutrition-related diseases. In addition, open formula diets can be purchased by government agencies via the advertised process. On the average, a 30 percent savings is realized by using this process as compared to procuring diets on a sole source basis. The total savings to NIH research programs resulting from using open formula diets is approximately \$150,000 per year.

Areas of research also conducted by the nutrition program include identification of the nutrient requirements of various stocks and strains of rodents, the characterization of animal models and the development of diets for animal species being introduced to biomedical research as new models.

## NUTRITION RESEARCH TRAINING

### Extramural Research Training

Within the extramural program, two basic mechanisms are used for nutrition training support: institutional awards and individual awards. In FY 1984, \$2,802,000 was expended to train 341 persons in nutrition.

Examples of areas in which the extramural trainees carried out their work include the following:

- o Nutrition and metabolism
- o Experimental and clinical nutrition
- o Clinical nutrition for physicians
- o Graduate training in nutrition
- o Development of time budgeting, energetic constraints
- o Role of thermogenesis in body weight regulation
- o Control of food intake: focus on nutrition and behavior
- o The influence of gastrointestinal signals on satiety
- o Nutrition and nephrology
- o Protein, amino acid, and urea metabolism in humans
- o Mechanisms of protective effect of dietary protein
- o Function of protein S, a new vitamin K-dependent protein
- o Differentiation of proteins in cultured mesothelium
- o Infectious diseases/basic microbiological mechanisms
- o Human interferon deficiencies in pediatric patients
- o Carcinogenesis and drug development
- o Multidisciplinary oncobiology
- o Nutrition and oncology: prevention and intervention
- o Experimental oncology and nutrition
- o Sympathetic regulation of fat metabolism during sepsis
- o Research in burns and trauma
- o Nutrition metabolism with trauma
- o Multidisciplinary heart and vascular disease research
- o Plasma lipoproteins and apoproteins
- o Nutrition-behavioral cardiovascular disease prevention
- o Interdisciplinary training program in lung disease



- o Postdoctoral training in lipid research
- o Nutrition, lipid metabolism, arteriosclerosis, and atherosclerosis
- o Lipid, lipoproteins, and atherosclerosis
- o Genetics of atherosclerosis
- o Characterization of postprandial lipoproteins
- o Dietary fat in lung microvascular injury from oxygen
- o Lipoprotein methodology, structure, and function
- o Chemistry of lipoproteins and atherosclerotic lesions
- o Cardiovascular epidemiology, biostatistics, and nutrition
- o Cardiovascular disease prevention
- o Cardiovascular pathology
- o Cardiovascular pathophysiology and biochemistry
- o The role of the liver in cholesterol ester metabolism
- o Target organ insensitivity to  $1,25-(OH)_2-D_3$
- o Metabolism of  $1,25-(OH)_2-D_3$
- o Regulation of  $25-(OH)_2-D_3$ -1-hydroxylase
- o Vitamin D metabolism during pregnancy and lactation
- o Intestinal absorption and metabolism of riboflavin
- o Biotin: the mechanism of carboxylation
- o Maternal nutritional status and plasma volume expansion
- o Thermal aspects of maternal care in deer mice
- o Nutrition and perinatal biology
- o Nutrition and growth and development
- o Training in neonatal biology
- o Cultural and environmental factors affecting child malnutrition: Sudest Island Region, New Guinea
- o Fatty acids as an energy source in pregnancy and in the neonate
- o The role of biological rhythms in reproductive behaviors, cellular growth, and differentiation related to the biology of the neonate
- o The interrelationships between body metabolism and puberty
- o Nutrition and oral health
- o Effect of high levels of fluoride on developing tooth enamel
- o The role of pigment epithelium in supplying phospholipids or their precursors, including fatty acids to retinal photoreceptor cells
- o The role of zinc and vitamin A deficiencies independently and together in the development of the structure and function of the fetal retina and the level of retinal vitamin A
- o Vitamin A and epithelium glycoprotein synthesis
- o Vitamin A status at various gestational ages
- o Mediation of endotoxin effects on zinc and copper metabolism
- o Effect of fluoride and calcium++ on amylase secretion

### Intramural Research Training

Within the NIH intramural program, 53 scientists were supported at an obligation of \$428,000.

Descriptions of the research carried out by both the extramural and The intramural trainees worked in the following areas:

- o Starch metabolism in patients with glycogen storage disease
- o Basic chemical defect in cystinosis in order to develop new and improved methods of treatment and diagnosis
- o Development and evaluation of better means of diagnosis and treatments for the inborn errors of metabolism
- o The kinetics of calcium metabolism in normal prepubertal children and the evaluation of disease-related changes in calcium metabolism in both children and adults
- o Effects of a thiamine deficient diet and ethanol on fetal development in an animal model
- o Role of magnesium in fetal and postnatal maturation, and in the treatment of infants with apnea
- o Pathophysiology of fibrodysplasia ossificans progressive and therapeutic intervention with 13-cis-retinoic acid
- o Nutrition induced alterations in metabolism
- o Control of macromolecular synthesis during normal growth as well as nutritional deficiency
- o Renin-angiotensin system and aldosterone regulation
- o Biochemical studies of hepatic and intestinal function
- o The anatomic and physiological causes of the absence of satiety in Prader-Willi syndrome
- o Pathophysiology of the adipocyte in human obesity
- o Effect of overfeeding on glucose disposal
- o Insulin regulation of glucose transport and metabolism
- o Hormonal regulation of cellular metabolism in order to define the defect in glycogen metabolism resulting from diabetes and to elucidate the mechanism of action of insulin
- o Diabetes and other chronic diseases in U.S. Indians
- o Lipoprotein metabolism in Pima Indians
- o Vitamin D resistance and related disorders.

## APPENDIX D

### RESEARCH ON NUTRITION AND PREVENTION OF DISEASE



## RESEARCH ON NUTRITION AND PREVENTION OF DISEASE

Research on the role of nutrition in disease prevention is supported by all NIH Institutes, except NIGMS. In FY 1984, support in this area totaled \$120 million or 62 percent of the total expenditures for nutrition research.

The definition for prevention used by the NCC for data retrieval are as follows:

- o Primary prevention. Actions to promote health or undertaken prior to the development of disease; i.e. studies on nutrients to define nutritional requirements for health maintenance.
- o Secondary prevention. Detection of disease in its early (asymptomatic) stages and intervention in order to arrest its expression; i.e., the use of a low phenylalanine diet in children with phenylketonuria in order to prevent mental retardation.
- o Tertiary prevention. Intervention after the development of a clinically manifest disease in order to reverse or arrest its progression; i.e. studies on sodium excretion for the treatment of hypertension and on low sodium diets for the treatment of the "salt-sensitive" hypertensive.

Prevention of disease begins early in life and involves many factors including the metabolic, cultural and behavioral aspects of nutrition and their effects on the nutritional status of infants and children. Investigators continue to attempt to define nutritional requirements of the fetus and neonate in order to prevent intrauterine growth retardation and to assure optimal fetal development, and the birth and subsequent growth of healthy babies.

### NEONATAL/INFANT NUTRITION

Optimal nutritional therapy is important for the physical, mental, and functional development and overall health and survival of premature infants in the face of biochemical immaturity; for infants and children with inborn errors of metabolism; and those infants with certain diseases or conditions, such as lactose intolerance, celiac disease, necrotizing enterocolitis, food hypersensitivity, and other diarrheal and malabsorptive conditions. Thus, in order to better understand what constitutes optimal nutrition therapy for the newborn, studies are under way on human milk and human milk banking in order to identify and preserve specific components of human milk and colostrum for potential use in the nutrition therapy of high risk infants.

The metabolic alterations and changes in umbilical uptake of nutrients that occur as growth retardation develops are unclear. Research is under way to better define nutritional requirements of the fetus and neonate so as to prevent intrauterine growth retardation and to assure optimal fetal development. Studies are examining the effects of nutritional supplementation on intrauterine growth retardation



which appears to be caused by an inadequate flow of nutrients and oxygen from the mother to the fetus across the placenta. Since some types of growth retardation may be reversible by providing parapla-cental nutritional supplements, investigators are evaluating the effects of long-term nutritional therapy on intentionally growth-retarded sheep fetuses.

The macrosomic infant is most commonly the product of a diabetic mother, an obese mother or one with gestational carbohydrate intolerance. A study using this infant as a model is investigating the mechanisms that contribute to excessive fetal intrauterine growth. Dietary and medical interventions are being evaluated and correlated with hormonal contributions to macrosomia in order to formulate reasonable antenatal predictors of excessive growth at a stage in pregnancy when intervention may be effective in reducing fetal and maternal morbidity. The goals of this study are to reduce maternal and fetal morbidity of patients at risk, to improve dietary control and medical management of these infants, to develop an understanding of hormonal mechanisms acting on fetal growth, and to develop predictive indices for excessive fetal growth at an early stage of pregnancy.

One hypothesis being tested in diabetic mothers is that maintaining normal blood sugar concentrations during pregnancy, particularly in the first trimester, will decrease fetal congenital malformations and neonatal morbidity and mortality. Such studies will increase our basic understanding of the physiology and pathophysiology involved in the diabetic pregnancy, and thereby help to decrease fetal and neonatal deaths and morbidity in the offspring.

A study is underway to determine if iron therapy can prevent or correct the developmental deficits and behavioral abnormalities associated with iron deficiency anemia of infancy by considering the levels of iron depletion at which infant behavior is adversely affected, by determining if there are differences between injectable and oral iron in behavioral effects, to determine if iron therapy can completely correct the deficits, and to confirm the specific patterns of behavioral disturbances observed in iron deficient anemic infants. The results of this study will help to guide practical pediatric and public health decisions about preventive strategies, screening priorities, the level of iron deficiency requiring treatment, and the best mode of therapy for iron deficiency anemia.

Recent studies on the cellular immune system of the normal human newborn infant have identified significant and selective maturational deficiencies. They include defects in specific cytotoxic and natural killer activities of the infants' blood. The specific regulatory mechanisms and cellular interactions underlying these defects need to be defined. Research in this area has specific implications for optimal infant feeding practices, since infant formulas lack the immunological factors and other antimicrobial components present in breast milk and important to the prevention of neonatal infections.

Vitamin E has been known to prevent the hemolytic anemia of prematurity often caused by a lack of this vitamin and to have beneficial effects on retrolental fibroplasia and bronchopulmonary dysplasia. Higher doses of vitamin E in preventing or modifying the course of bronchopulmonary dysplasia in infants are being investigated, while animal studies are comparing the role of different antioxidants (vitamin E, ascorbic acid, and beta carotene) in modifying the antioxidant enzymes and levels of glutathione. The clinical and immunological status of premature infants on diets, with or without supplemental vitamin E, is also being examined through a number of immunological tests to establish whether presently used doses of vitamin E have beneficial, deleterious, or no discernable effects.

In order to better understand vitamin A related disorders and optimal intakes of vitamin A and protein during pregnancy, fetal, and neonatal life, studies are under way to examine the effects of various intakes of vitamin A and protein on retinol homeostasis. Results of this research will provide useful information for the prevention of vitamin A related disorders during pregnancy, neonatal life, and in childhood.

In studies of protein calorie malnutrition in neonates and infants, the pathogenic mechanisms responsible for impaired leukocyte and/or monocyte mobilization are being evaluated, since these infants are at high risk of developing systemic infections resulting from impaired tissue mobilization of phagocytic cells. Functional requirements of serum complement proteins and/or specific IgG globulin are being determined by studying the influence of deficiencies of complement proteins and/or specific IgG in the serum of neonates or infants with protein-calorie malnutrition. Results of this research will provide new information on the clinical relevance of in vitro abnormalities of biologic functions of phagocytes, identify clinical risk factors in high risk pediatric hosts, and provide the framework for therapeutic pharmacological approaches to inflammatory disorders in these children.

Dietary zinc is being examined in the mouse model for its effects on lymphocyte function during different stages of development in the mouse model; i.e., the effects of suboptimal dietary zinc levels on the development of immunity during the fetal/neonatal period will be investigated since preliminary evidence suggests that zinc deficiency during ontogeny alters lymphocyte development.

Research is under way to obtain better information on the amount and type of vitamin D metabolites required by neonates for proper skeletal mineralization at various gestational ages. This data could result in a redefinition of the vitamin D requirement for the low birth weight and/or premature neonate which would in turn help to define more appropriate synthetic formulas for the developing newborn.

Parameters of growth and development of infants fed various formula and those breast fed are being studied in normal infants as well as low birth weight infants. Investigations of normal infants involve

the study of energy expenditure, the interaction between nutrients, and the various factors that may influence food consumption. To study the appropriateness of different feeding regimens for the low birth weight infant, studies are under way on body composition, anthropometric measures, and the immunological development of the infant. These studies will provide additional information on the possible benefits of feeding the low birth weight infant with human milk.

Research on human milk, colostrum and human milk banking provides important data for the development of the best possible nutritional therapy of high risk infants. A number of projects are under way to examine the unique properties of human milk, by characterizing the biological interactions of milk components at the interface of milk with the gastrointestinal lumen. One project is evaluating the protective effects of milk phospholipids on maintaining the integrity of the gastrointestinal tract and thereby preventing necrotizing enterocolitis.

Because of the similarities of infant botulism with sudden infant death syndrome (SIDS), it seems evident that infant botulism may be caused by the various toxin producing clostridia that colonize the infant gastrointestinal tract and cause SIDS. Research is under way to identify the host-environmental risk factors for SIDS in order to design preventive measures applicable to infant botulism and other toxigenic intestinal infections of infancy. Human milk has been shown to offer protection to the infant against toxigenic illnesses.

#### NUTRITION DURING EARLY CHILDHOOD

Studies are investigating the influence of specific nutrients on the toxicity of heavy metals in children and the application of a computerized EEG as a method to enhance the reliability and validity of nutritional and environmental influences on brain development. The question as to whether certain nutrients protect against the effects of heavy metal toxins or whether specific food substances potentiate the toxic effects on cognitive and brain function is being addressed. Between the ages of 2-5 years, lead may be particularly harmful since this is a period of rapid brain and cognitive development. Therefore, data on lead toxicity during this age period is being collected. Findings from this research will significantly enhance our understanding of the importance of early diagnosis and appropriate treatment of heavy metal toxicity in children.

Schistosoma hematobium infection and its treatment are being studied in school children in Kenya in order to determine the extent to which this infection contributes to anemia and retarded physical growth of these children. The cost and feasibility of routine treatment of schistosomiasis in primary school children will be assessed in terms of its effectiveness in preventing anemia and growth retardation.

Tooth decay affects most children as soon as primary teeth erupt. By 12 years of age, the average American child has four teeth attacked by caries, while by 17 years of age, eleven teeth are decayed.



Prevention efforts are aimed at making teeth less susceptible to caries by the use of fluorides and by decreasing the frequency of sugary foods.

Many studies are under way to investigate how chronic high levels of fluoride, supplied in the drinking water, affect the developmental stages of enamel formation and mineralization. The calcium, phosphate, fluoride, and protein contents of the enamel are being determined in terms of enamel weight and volume, and the composition of the matrix. A 5-year longitudinal clinical trial is under way to determine whether prenatal fluoride supplements are effective in preventing the development of caries in primary dentition. Pregnant women in the first 3 months of their pregnancy are being given supplemental fluoride (1 mg/day), and their offspring will be followed with a dental examination at their third and fifth birthdays.

In another study, use of fluoride tablets and rinses are being assessed for their effectiveness in preventing dental caries in children over an 8-year period beginning in kindergarten. Additional investigations are examining the general safety of excessive as well as deficient amounts of fluoride given to infants and toddlers, and the possibility that beneficial effects other than dental caries reduction may result from optimal intakes.

The role of fluoride in bone resorption, formation and metabolism; lipid metabolism; caries prevention; and its relationship to other trace elements is being elucidated. Investigations are under way on calcified tissue metabolism, the relationship between skeletal fluoride load and plasma fluoride levels, levels of nonionic fluoride in human and nonhuman serum, as well as the general metabolic effects of fluoride after exposure to high and low fluoride exposure.

Numerous investigations are being carried out on the biochemical manifestations of genetic diseases in children, i.e., on the interrelations of intermediary metabolism and the pathogenesis of the clinical manifestations of the inborn errors of metabolism, including ketotic hyperglycinemia syndrome and hyperuricemia, transient hyperammonemia of the newborn, methylmalonic acidemia and homocystinuria, and the organic acidemias. Other studies are evaluating nutritional therapy of infants and children with inborn errors in terms of its effectiveness in preventing or ameliorating the full expression of these genetic disorders. The therapy aims to minimize the patient's exposure to harmful nutrient substrates and to provide essential nutrients in required concentrations.

Maternal phenylketonuria produces a high incidence of children with mental retardation, growth retardation, microcephaly, and congenital malformations, particularly cardiac defects. The effects of maternal phenylketonuria on pregnancy outcome is being investigated in order to determine the level of maternal phenylalanine that will maintain a normal pregnancy, at what stage of pregnancy a low phenylalanine diet is most effective in preventing the effects of maternal PKU on the developing fetus, and if the beneficial effects of a low phenylalanine diet can be improved when initiated prior to conception com-

pared to post-conception. In order to develop more effective dietary regimens for the treatment of maternal PKU, studies are under way to investigate a new treatment which involves the administration of valine, isoleucine, and leucine (VIL). The effects of this treatment in preventing the intrauterine damage that accompanies maternal PKU is now being tested in rats with maternal PKU. This data will lay the groundwork for human trials of VIL treatment in pregnant women.

Studies on the discontinuation of the low phenylalanine diet in PKU children are under way since the mental retardation that often comes with the disease is thought to be preventable by dietary therapy initiated during the first month of life and carefully monitored during subsequent years. Differences in physical, neurological, and growth parameters of children kept on the diet for various periods of time are being assessed in order to develop the most appropriate dietary treatment for these PKU children.

In studies of other inborn errors, investigators are attempting to develop effective methods of treating infants and children with hyperammonemia such as those with Reye's syndrome, portal systemic encephalopathy, organic acidemias, etc. The long-term neurodevelopmental consequences of low grade neonatal hyperammonemia in low birth weight children are being studied by developmental and psychological methods.

Studies on the effects of malnutrition and environmental deprivation on child development are under way to determine the extent to which it is possible to prevent physical and psychological growth retardation by food supplementation and maternal tutoring.

In an attempt to prevent adult obesity, studies are under way to determine the etiology of obesity in childhood. Investigations designed to evaluate the relative contributions of genetics, in utero factors, and nutritional factors to the pathogenesis of childhood obesity are under way in infants born to diabetic mothers and either breast- or bottle-fed. Parallel longitudinal studies also are being performed in obese and normal weight monozygotic and dizygotic twins. Investigators are examining the association of childhood obesity with prior eating practices and physical activity and parental attitudes, and infant body measurements and sociocultural factors in order to identify critical periods of obesity development.

The role of diet, physical training, and behavior therapy in the treatment of childhood obesity is also being examined through measures of body composition, cardiovascular function and metabolism. The results of this research will further understanding of the mechanisms underlying obesity and determine how diet and/or exercise induced weight loss affects the physiological abnormalities of childhood obesity. Since overweight children are more apt to become overweight adults, programs to prevent adult obesity must involve the development and evaluation of methods to control body weight in high-risk children. Investigators are examining the effects of relationships between parents and children in terms of food intake, energy expenditure, and habit and behavior patterns in order to



establish the extent to which parental modeling and shared familial patterns affect the development of obesity.

Other studies to determine appropriate behavioral treatment programs for childhood obesity consider gradual and long-term changes in habit through stimulus control, reinforcement, self-management training, and other behaviorally oriented procedures. These procedures are designed to facilitate the maintenance of behavior change that includes the modification of both food intake and energy expenditure and thus produces lasting weight loss. This research should prove useful in understanding the mechanisms responsible for the development of obesity in children, and in tailoring treatments to fit the characteristics of the children and their families.

#### ADOLESCENT NUTRITION

Studies of adolescents investigate the nutrient requirements during puberty and adolescent pregnancy, as well as the problems of obesity, bulimia, and anorexia nervosa. Behavioral and cultural aspects are being investigated for their effect on the development of deleterious adolescent eating habits. Much of the research on nutrition and prevention is devoted to the development of healthy adolescents who can attain their genetic potential without malnutrition or obesity.

Adolescent obesity is being examined in terms of differences in resting metabolic rate, daily energy expenditure, and the thermogenic and hormonal responses to overfeeding in obese versus nonobese adolescents. Results of this research will help clarify whether obese adolescents are capable of dissipating excess carbohydrate calories as effectively as the nonobese adolescent and whether reduced energy expenditure is an etiologic factor in the onset or persistence of adolescent obesity.

Measurements of subcutaneous fat thickness and estimates of total body fat from persons from birth through age 60 are being analyzed in order to determine the normal pattern of fat deposition and loss for this age range, to determine the predictors of obesity in childhood and at older ages, to determine the causation (familial, genetic, etc.) and significance of obesity in infancy and at other ages, and to provide equations that estimate total body fat from anthropometric variables.

In order to examine the effects of the early predictors of coronary heart disease, a 3-year longitudinal study is under way which includes examinations of black and white adolescent males for possible relationships between changes in adiposity, sex hormones, lipids, lipoproteins, and apolipoproteins. A similar study is being conducted in adolescent male offspring of parents with premature coronary heart disease, myocardial infarction, and/or coronary bypass surgery. Various parameters to be examined in terms of their relation to the development of CHD include determining whether: offspring of patients with premature heart disease have different lipid, lipoprotein, and apolipoprotein profiles placing them at increased risk; differences exist in the lipid profiles in black and

white males; significant decreases occur in HDL cholesterol during sexual maturation related to interactions between testosterone, estradiol and ponderosity; sex hormone profiles in males with early CHD differ from healthy controls; and mean estrogen levels in obese males are significantly different from nonobese males.

Investigations are also under way to determine if dietary interventions started early in life can influence the development of spontaneous atherosclerotic lesions, and the metabolic response to dietary cholesterol consumed in adulthood. It is hypothesized that early stimulation of cholesterol catabolism increases hepatic cholesterol-7- $\alpha$ -hydroxylase activity that persists in adult life and therefore influences the atherogenic response.

Since cardiovascular disease (CVD) is thought to begin early in life, intervention prevention programs are designed for young people that may help to prevent the later occurrence of CVD. A number of studies are examining the impact and effectiveness of family-based interventions to alter behaviors thought to be linked to risk factors associated with CVD. One program is under way to implement and evaluate a comprehensive educational program in the schools which alters the behaviors related to cardiovascular risk of children and their parents. The risk factors to be addressed include nutrition, smoking, and blood pressure management. It is thought that a comprehensive risk factor program aimed at both children and parents is likely to have a greater impact on health status with changes sustained over time.

#### ADULT NUTRITION

In order to better understand the kind of preventive measures appropriate to the nutritional needs of the elderly, a number of studies attempt to elucidate the nutritional requirements with age and the effect of body weight on health status in terms of longevity and disease status. Other studies are examining the behavioral effects of undernutrition and aging, and the effects of various living arrangements on dietary habits, stress, and subsequent nutritional status of the elderly. The effects of nutritional status on immune function, i.e., the effect of protein malnutrition as well as of tissue levels of a large number of nutrients on immune function, are under investigation. One study in mice has shown that dietary restrictions beginning in mid-adulthood can bring about immune rejuvenation and extend life span. Nutritional manipulations are being used to chronologically delay aging in rats and to probe the aging processes.

Research on nutrition and prevention deals with nutrition's role in the prevention of specific diseases such as cancer, coronary heart disease, atherosclerosis, hypertension, diabetes, osteoporosis, diverticulosis, dental caries, etc.

#### CANCER

Epidemiological studies carried out in various population groups within the United States such as the Seventh-Day Adventists, Japanese, and migrants, and those carried out in other countries such as Finland, China, Colombia, and France have provided important information on the possible impact of different dietary regimens along with lifestyle characteristics on cancer etiology. These epidemiological studies provide clues that in combination with sophisticated laboratory and clinical experimentation, have been instrumental in increasing our knowledge of the mechanisms of action of specific nutrients in the etiology of cancers of the breast, colon, skin, pancreas, liver, etc.

A number of studies investigate the effect of specific nutrients and food components on the initiation, promotion, and inhibition of carcinogenesis and their possible role in the prevention of cancer. Many studies have shown that vitamin A compounds, their derivatives, and analogues, i.e., the retinoids, may prevent or reverse carcinogen-induced malignancies. Investigators are currently attempting to develop new retinoids with improved chemopreventive activity, lowered toxicity, and superior pharmacokinetic properties. In order to explore the effects of structural modification at or near the polar terminal group and at the cyclohexenyl group on chemopreventive activity, studies are examining the derivatives of retinoids, such as retinol and retinoic acid with known activity, and new types of retinoid structures. These new retinoids will be evaluated for their chemopreventive activity through pharmacological investigations and biochemical studies.

One clinical trial is investigating the effectiveness of the synthetic retinoid, N-4-hydroxyphenyl retinamide (HPR), on preventing contralateral breast cancer in women already operated on for a breast tumor. HPR is a derivative of retinoic acid which has been shown to inhibit N-nitroso-N-methylurea induced mammary carcinogenesis, to exhibit an antiproliferative effect on rat mammary epithelium, and to block the combined proliferative effects of insulin and prolactin upon the mammary epithelium growing in vitro.

Another study is examining the inhibitory effect of combined treatment with 13-cis-retinoic acid and alpha-difluoromethylornithine (DFMO) on 12-O-tetradecanoylphorbol-13-acetate promoted skin tumors. It is hypothesized that the combination of these compounds may show enhanced inhibition of skin tumor promotion at dosage levels below the threshold for undesirable side effects of each when used singly. Such studies will provide important information on the possible combined use of these compounds for the prevention or treatment of human cancer.

The effects of oral administration of beta-carotene alone or in combination with alpha-tocopherol and ascorbic acid are being examined for chemopreventive effects in patients at high risk of developing basal cell carcinoma. Results of one study of melanoma indicated that the risk of melanoma decreased with increases in plasma levels of beta-carotene, alpha-tocopherol and retinol, or in red cell selenium.



Vitamin E and folate are being studied for their roles in liver function and the prevention of carcinogenesis; vitamin E has been proposed to function by quenching free radicals generated primarily as a result of oxygen metabolism. The presence of free radicals in tissues is believed to result in physiological deterioration which is manifested by aging, coronary heart disease, connective tissue disorders, and tumorigenesis. The mechanisms of vitamin E in the prevention of mammary cancer induced by daunomycin are also being explored by determining the effects of alpha-tocopherol on xanthine oxidase and the quinone reductase activity. Since the liver functions as a storage site for folates, other investigators are looking at the factors and conditions that control the storage and release of folate coenzymes in the liver, and what effects the anti-folates utilized in cancer chemotherapy may have on this process. Numerous studies are investigating the flavonoids in order to determine their exact role in inhibiting carcinogenesis.

Studies on the role of fat, especially levels of unsaturated fatty acids in the diet, attempt to provide more insight into the mechanisms of induction and promotion of cancer, as well as the simultaneous physiological effects observed with cyclopropanoid fatty acids.

High levels of dietary fat have been shown to promote murine mammary tumorigenesis in virtually every rodent mammary tumor model examined, although the exact mechanisms by which this occurs are not known. One novel mechanism currently being examined is that high levels of dietary fat enhance mammary tumorigenesis directly by interfering with mammary intercellular communication or metabolic cooperation between cells.

Clinical trials are under way to examine the effects of a low fat diet (20 percent of the calories) on breast cancer incidence. One trial is investigating the effects of this diet on disease relapse and overall survival in stage II breast cancer patients receiving chemotherapy after primary surgical treatment, while other trials are studying the same dietary regimen in the development of breast cancer in high risk postmenopausal women, as well as in a group of women whose annual risk of breast cancer is estimated to be about one percent.

Data from various studies suggest that the effects of dietary factors on the risk of breast cancer act through alterations in the hormonal milieu, especially in the teenage years when the breast is thought to be particularly sensitive to carcinogens. A study to examine the relationship of dietary intake, ovulatory status, and serum hormone levels, i.e., levels of unbound and albumin-bound serum estradiol and testosterone, is under way in vegetarian and nonvegetarian teenage girls. The results of this study will be used as the basis of an intervention trial to study the effect of changes in diet on hormonal balance in teenagers.

Other possible chemopreventive agents being examined for activity against breast cancer include various levels of vitamin C and selenium.

Epidemiological studies suggest that populations consuming high fat diets are at an elevated risk of pancreatic cancer development. Investigators have shown that pancreatic cancer in Syrian hamsters is enhanced when high levels of dietary fat (corn oil) are fed after a single dose of the pancreatic carcinogen N-nitrosobis-(2-oxopropyl)-amine (BOP). Additional studies using the hamster are under way in order to investigate whether the enhancing effect of the diet is related to the fat per se or to the increased calorie intake of the animals fed the high fat diets, whether the type of fat is important in the promotion of pancreatic cancer as shown for other types of experimental and human cancer, and what is the mechanism by which dietary fat promotes cancer in the pancreas.

In order to establish the mechanisms by which the types of dietary fat may affect the initiation and promotion of colon tumors, the following specific investigations are under way: the dose-response effect of different amounts of corn oil or lard in the diet is being compared in terms of initiation and promotion; the threshold level at which the types of dietary fat exert measurable effects on colon cancer is being examined; the effects of types of dietary fat on initiation of colon carcinogenesis are being assessed using carcinogen metabolism and DNA methylation as indicators; the effects of types of dietary fat on the promotion of colon carcinogenesis are being assessed using colonic secondary bile acids and 7-alpha dehydroxylase as indicators; and the effects of types and levels of fat on prostaglandins and prostaglandin synthetase activity of colon tumors are being examined.

Other studies of tumorigenesis in the large bowel have shown that diets high in cholesterol or drugs which increase cholesterol disbursement within the gastrointestinal tract are associated with increased tumorigenesis. A study is under way to define precisely the stage of action, if any, of dietary cholesterol in cancer promotion.

Since nutrient deficiencies, excesses, and imbalances may play a role in the etiology of colon cancer, a study is under way to examine the interaction of selenium, vitamin E, saturated fatty acids (SFA), and polyunsaturated fatty acids (PUFA) in colon carcinogenesis. Specifically, this study considers the role of dietary excess, adequacy, or deficiency of selenium and vitamin E, individually and in combination, on colon carcinogenesis in rats fed diets with various levels of SFA and PUFA.

A wide variety of fruits, vegetables and their byproducts are being analytically screened for compounds and classes of compounds known to inhibit carcinogenesis. Attempts are being made to isolate novel antineoplastic agents from higher plants including members of the Cruciferae, Umbelliferae, Allium, and Leguminosae families. One study involves isolation of possible chemopreventive agents from the cabbage and pea through short-term assays for antigenotoxic and antipromotor activities. Two flavonoid derivatives of benzylisothiocyanate and indole-3-carbinol, robinetin and apigenin, respectively, are being examined in order to better define the chemopre-



ventive action of these compounds. All partially purified substances will be assayed for their ability to inhibit skin tumorigenesis.

In addition, cancer inhibitors in the diet, such as butylated hydroxyanisole (BHA), cinnamic acids, coumarins, aromatic isothiocyanates, indoles, and their derivatives are also being tested. One study is examining active components in onion and garlic oils, including the aliphatic di- and tri-sulfides, for their ability to inhibit the promotion of mouse skin tumorigenesis. Edible plant sources of, and quantitative analytical methods for, compounds such as ellagic acid, flavonoids, coumarins, isothiocyanates, and indoles are being investigated. The identification of nontoxic cancer inhibitors in higher plants may provide a variety of agents with the potential of preventing human cancer and will provide a better understanding of the total inhibitor activity and their mechanism of action present in the plants.

Chemopreventive agents such as the flavonoids, disulfiram, ascorbic acid, selenium, glutathione, phenolic antioxidants, and protease inhibitors are being examined for their interactions with a variety of chemical carcinogens and the resultant chromosomal instability. Quantitative assays of the chemopreventive agents are being used to determine which agents inhibit tumor induction at specific stages, as well as the mechanisms of action.

Alcohol has been implicated as either a direct or indirect carcinogen in cancers of the oropharynx, esophagus, and liver. Recently, a positive correlation between alcohol and breast cancer has been shown in women. It is generally assumed that alcohol modulates the carcinogenic response to other chemicals and therefore may act as an initiator or promoter of carcinogenesis.

Animal tumor models are being studied to help confirm alcohol's role in the enhancement of carcinogenesis. Some of these models are examining whether alcohol enhances the initiation of hepatocytes by dimethylnitrosamine, esophageal cells by methylbenzyl nitrosamine, and mammary cells by 1-methyl-1-nitrosourea and dimethylbenzanthracene, or whether alcohol acts as a promoter when administered after these initiating agents. Specific studies are designed to determine the effects of ethanol, as well as of whiskey and wine, on the initiation and promotion of carcinogenesis in these models. Others studies on the role of alcohol in cancer are testing whether beer and ethanol consumption increase large bowel carcinogenesis through an increase in the fecal levels of bile acids, neutral sterols, and other known cancer promoters. The action of ethanol in promoting the carcinogenic effect of tobacco in the etiology of head and neck cancer is also being examined.

Preliminary investigations of wine consumption suggest that many red wines contain high levels of direct-acting mutagens, and that a strong dose-dependent epidemiological correlation appears to exist between the consumption of red wine and the occurrence of stomach cancer in France. A study on the origin, distribution, and control of mutagens in wine is attempting to determine the distribution and

chemical identity of mutagenic compounds in red, rose, white, and dessert wines as well as brandies; to define the production parameters which determine the level of mutagenic activity present in wine; and to devise procedures for the selective removal of mutagens from wine. The influence of winery practices (including high pressure pressing of grape skins, mechanically abrasive juice recirculation methods, and refining treatments) on wine mutagenicity is being evaluated.

These studies will help to resolve many of the conflicting reports on the effects of chronic alcohol consumption on the carcinogenic process, as well as contribute to the development of medical strategies to reduce the risk of alcohol carcinogen interactions at the clinical level.

Caffeine (1,3,7-trimethylxanthine) is the most widely used psychotropic drug in North America, however, its possible contribution to malignant disease has not yet been determined. Studies involving animal models of human breast cancer are making attempts to determine whether or not chronic caffeine consumption contributes to the genesis and/or progression of mammary gland neoplasias. In addition, the potential interaction of caffeine with high levels of dietary fat is being examined since it is important to examine whether chronic caffeine consumption can significantly influence the mammary tumorigenic activities of high fat diets. The primary impetus for this research was generated by a consistent observation of a mild but significant promoting effect by caffeine of rat mammary gland carcinogenesis *in vivo*.

Studies have shown that green coffee beans induce a marked increase in the activity of the glutathione (GSH) S-transferase system which can detoxify a wide range of xenobiotic compounds, including chemical carcinogens. Roasted coffee beans have a comparable inducing effect, while instant coffee is approximately half as potent. About 40 percent of the inducing activity of green coffee beans has been linked to two diterpene esters which have been isolated and identified from kahweol palmitate and cafestol. Additional work with these two compounds will consider structure-activity relationships that induce increased GSH S-transferase activity; their effect on carcinogen-induced neoplasia; and the development of sensitive techniques for quantitating the diterpene esters in coffee beans, instant coffee, and coffee beverages as consumed. The widespread distribution of diterpenes, which are common constituents in plants, enhances the importance of ascertaining the capacities of these compounds to inhibit neoplasia.

Studies of mineral interactions during carcinogenesis have revealed that magnesium inhibits lung adenoma formation in lead and nickel treated strain A mice, as well as in cadmium and nickel induced sarcomas in rats. Part of the protection afforded by magnesium against the tumorigenic activity of cadmium and nickel is due to the diminished accumulation of the carcinogenic metal at the target site. In chemical studies, magnesium, zinc, and calcium inhibited cadmium binding to DNA. Extension of the possible antagonistic effects of

the physiologically essential divalent metals against tumor formation by nickel, lead, and cadmium in other target sites are being explored. Numerous studies are under way to examine the effects of zinc as well as selenium in preventing tumor growth.

Other studies are under way to examine the hypothesis that low levels of dietary protein intake are associated with a decrease in aflatoxin B<sub>1</sub> induced liver tumor incidence due to events occurring during the postinitiation phase.

A project is under way to develop a pilot data base on cancer chemoprevention testing in experimental animals that may be used as a model for future data base development efforts of chemopreventive agents. This effort involves a compilation of the literature on prospective chemopreventive agents such as vitamin A and its analogs, vitamin C, vitamin E, selenium and an analysis of the literature for specific parameters in order to facilitate the development of test protocols for chemopreventive agents using established criteria.

Efforts are also under way to develop more appropriate nutrition intervention strategies in conjunction with chemotherapy, radiation, and immunotherapy regimens in order to better manage the cancer patient. Studies have shown that a nucleotide free diet may enhance the effects of chemotherapeutic agents in autoimmune, neoplastic, and viral disease states.

Long-term cancer prevention strategies that provide information on the role of diet and smoking are being examined in adolescents in terms of their effect on changing behaviors related to these risk factors and thereby preventing cancer later in life.

#### NUTRITION AND HEART DISEASE

A number of studies investigate the risk factors of cardiovascular disease in order to develop appropriate intervention strategies, either on a community or individual basis. Community demonstration studies have been successful in establishing coronary heart disease prevention programs in community organizational settings, churches, and schools. Attempts to modify cardiovascular disease risks are also being made through behavior programs designed for families. Specific dietary components such as alcohol and lipids are being studied in terms of their effects on coronary heart disease. Various kinds of material have been developed on blood pressure control, weight control, and smoking cessation. Research continues to investigate the long-term effects of these programs on cardiovascular disease morbidity and mortality.

Population studies have provided evidence for an inverse relationship between plasma high density lipoprotein cholesterol levels and the prevalence and incidence of ischemic heart disease. Furthermore, metabolic studies showing changes in HDL levels modulated by diet, drugs, hormones, exercise, weight loss, etc., indicate that a particular subfraction of HDL, namely HDL<sub>2b</sub>, is responsive to such inter-



vention. A study of normal men and women is under way to investigate the effect of diets varying in carbohydrate and fat on changes in HDL levels, and to examine the mechanisms whereby lipoprotein lipase and hepatic triglyceride lipase alter the plasma levels of HDL-cholesterol.

In studies on the effect of polycyclic aromatic hydrocarbons on the growth and development of aortic lesions, cholesterol feeding is being tested in terms of its effect on exacerbating lesion development. The addition of two active protease inhibitors to the diet, retinyl acetate and aspirin, is being tested for interference with lesion development. Results from this research will provide valuable information on the promotional nature of carcinogens in terms of the growth and development of spontaneous atherosclerotic lesions, and on the capacity of environmental factors including pollutants and dietary supplements in preventing atherosclerotic plaque formation.

Since epidemiological studies have provided evidence that populations consuming diets rich in the omega-3 fatty acids derived from marine animals have lower plasma lipid levels and increased bleeding times, studies are under way to examine the effects of various polyunsaturated fatty acids in normal and hyperlipidemic humans. Three different diets are being examined in one study: a high saturated fat diet; a high omega-3 fatty acid diet from salmon and fish oil; and a high omega-6 diet from safflower oil. To date, the high omega-3 diet appears to lower plasma cholesterol, LDL, triglycerides and VLDL, increase bleeding times and decrease platelet aggregation. Additional studies are designed to explore the mechanism of the hypotriglyceridemic and platelet effects of the omega-3 fatty acids in human subjects under controlled dietary conditions. The thrombocytopenic effect of dietary omega-3 fatty acids will be explored by radiolabeled platelet turnover studies.

Another study examining the effects of fish oil on atherosclerosis is under way in Cercopithecus acethiops (vervets). Pertinent questions to be explored are concerned with the effect of fish oil on plasma lipids, platelet and neutrophil lipid composition and function, and atherosclerosis. The incorporation of eicosapentaenoic acid into cell membranes, and the products of cyclooxygenase and lipooxygenase pathways are being studied in platelets and neutrophils along with the effects of the production of prostacyclin by the artery. The long-term effects of fish oil are being assessed and the amount of atherosclerosis are being determined morphometrically. Since this unique class of dietary fatty acids may potentially be important in preventing and treating atherosclerotic and thrombotic diseases, investigations are now under way to establish their mechanisms of action, long-term efficacy and possible untoward side effects.

Exercise is also being examined as an important therapeutic modality in preventing the deterioration of the cardiovascular system with age since the functional capacity of the cardiovascular system and the coronary artery disease risk factors are known to be influenced by a person's level of physical activity. The question as to whether

exercise can reverse the deterioration in glucose tolerance, lower plasma insulin levels, and induce favorable alterations in plasma lipid levels in older individuals is being examined.

The Pima Indians have a high prevalence of obesity, diabetes mellitus, and hyperinsulinemia; however, they have low plasma cholesterol levels, reduced low density lipoproteins synthesis, and a low incidence of cardiovascular disease. Lipoprotein metabolism in Pima Indians is being investigated in order to further understand its control and the influence of obesity and diabetes. A preliminary study of male Pimas indicated that a large proportion of VLDL is metabolized without conversion to LDL; this suggests the existence of an alternate pathway which might be the mechanism for the maintenance of low LDL levels in this population.

Studies of free fatty acid turnover have also been conducted in Pimas of varying body weights. Obesity appeared to be associated with an increased flux of free fatty acids without increasing plasma concentrations, a phenomenon which might account for the increased VLDL production in these individuals. The results of lipoprotein metabolic studies in Pimas to date suggest a large flux of substrates and regulators (i.e. insulin) which cause an overproduction of lipoproteins, but that compensatory mechanisms are operative which result in the maintenance of low plasma concentrations.

Since both obesity and diabetes are associated with changes in plasma lipoproteins and therefore may be related to the increased prevalence of cardiovascular disease, the lipoprotein profiles of obese and diabetic Pima Indians are being compared to the profiles of Caucasians participating in the Lipid Research Clinic survey. Total cholesterol, LDL cholesterol, and HDL cholesterol levels seem to be lower in adult Pimas than in LRC Caucasians, while total and VLDL triglyceride concentrations are higher. Total and VLDL triglycerides levels appear to increase with increasing obesity, whereas a strong negative association appears between obesity and HDL cholesterol. The lipoprotein profiles are being analyzed in relation to diabetes and CVD in the Pimas, and compared with data on Caucasians and other diabetic groups. The data collected thus far suggest that there are racial differences in lipoprotein distributions, which may be important in the determination of the prevalence of CVD.

Other studies in the Pima Indians are under way to determine whether their high incidence of obesity is due to a thrifty gene, one which predisposes them to store energy more efficiently. The results of research to date suggest that the obese Pimas, when compared to lean Pimas, achieve higher levels of norepinephrine during norepinephrine infusion, and that these levels are probably the result of a clearance defect for norepinephrine. Also, the thermogenic response to norepinephrine appears to be blunted after overfeeding in both lean and obese Pimas, while no such changes have been observed in Caucasians. Studies will investigate thermogenesis further by considering thyroid kinetics in lean Pimas and norepinephrine kinetics in both lean and obese Pimas.



Many studies are under way to determine the etiology and pathogenesis of atherosclerosis and its sequelae through morphological, experimental, epidemiologic, chemical, immunochemical, cytologic, and biometric methods. Cholesterol and lipoprotein metabolism is being investigated in primates to better understand the mechanisms responsible for large differences in serum cholesterol and lipoprotein concentrations. A new pathway through LDL is being studied in order to identify the molecular basis of cholesterol metabolism. In this pathway, LDL is bound at high affinity surface receptor sites of cells, the lipoprotein is internalized by endocytosis and the cholesterol is released for membrane synthesis. Other studies are examining the mechanisms of cholesterol synthesis in the liver, i.e., cholesterol feeding, stress, and diurnal lighting have been shown to alter the rate of enzyme synthesis of HMG CoA reductase. The role of diet (interactions between fat and cholesterol), genetics, and environmental stress in the pathogenesis and etiology of atherosclerosis is being studied in baboons.

Alfalfa meal or alfalfa saponins have been shown to reduce the intestinal absorption of cholesterol, lower cholesterolemia, and induce the regression of atherosclerosis in cholesterol fed monkeys. A series of synthetic saponins, e.g., cellobiose-tipogenin, cellobiose-diosgenin, glucose-diosgenin and glucose-tipogenin, have been shown to bind cholesterol in vitro and reduce intestinal absorption of cholesterol in rats. The effects of these synthetic saponins on atherosclerosis prevention is being studied in rabbits with atherosclerosis induced by a cholesterol diet or fed a cholesterol free diet. The effects of the synthetic saponins on cholesterolemia in monkeys will be studied, and if they reduce cholesterolemia without toxic effects, their use in the treatment of hypercholesterolemia in humans will be considered.

Studies of lipoprotein metabolism consider the effects of dietary factors (fat, cholesterol, and protein), gender, and sex hormones on lipoprotein composition and metabolism and on bile composition and formation. The relationship of abnormal carbohydrate metabolism and the development of endogenous triglyceridemia is also being examined. One study is under way in diabetic monkeys in order to determine their susceptibility to atherosclerosis as it relates to plasma lipoprotein levels or hormone levels of insulin, glucagon, and growth hormone. Attempts are being made to determine whether the diabetic state influences rates of LDL degradation and sites of LDL degradation in vivo. Special attention is being paid to the rates of LDL uptake in the arterial wall, since an abnormality here could contribute to the premature atherosclerosis associated with diabetes, even in the absence of hyperlipoproteinemias. The results of this research will provide insight on the determinants of cardiac disease in diabetes.

The Lipid Research Clinics provide data to improve the diagnosis and management of hyperlipoproteinemia through investigations on its causes and treatment. The SCOR program includes projects on lipid and lipoprotein metabolism, hyperlipidemias, atherogenesis, thrombosis and coronary heart disease, and focuses on the early natural history of atherosclerosis in children.

One study is under way to determine the effectiveness and acceptance of an "alternate diet" (low in cholesterol, saturated fat, total fat and sodium and containing increased amounts of complex carbohydrates, fiber and potassium), in preventing coronary heart disease and hypertension in a random sample of 233 families.

Projects are under way to study the precursors to and concomitants of changes in risk factors for coronary heart disease in young adults, as well as to track the predictors of high blood pressure in young children. This research will help to establish appropriate strategies for the prevention of coronary heart disease and hypertension.

## HYPERTENSION

Investigations continue to explore methods to prevent and control hypertension, a disease that affects approximately 60 million Americans. Interim findings from one study imply that a high proportion of individuals with mild hypertension may control their blood pressure if weight control and sodium restriction is achieved. Knowledge of specific risk factors for hypertension allows for the development of appropriate messages used in education and behavioral modification prevention programs. Two demonstration and education research studies are exploring the possibility that dietary changes and/or relaxation training will reduce or eliminate the need for medication in hypertensives, and that paraprofessionals and nonclinic settings such as the workplace and community sites are appropriate for the non-pharmacological treatment of hypertension.

A number of studies of hypertension control are under way in animal models in order to better understand the effects of diet and specific nutrients on the mechanisms of hypertension. One study examining potential mechanisms is investigating the protective effects of oral tyrosine against elevation of blood pressure in renal hypertensive rats. Additional studies will be carried out to assess the effects of chronic oral treatment with tyrosine on the development of experimentally induced hypertension, including DOCA induced and spontaneously hypertensive rats.

Two additional objectives of this research are to determine the effects of chronic intracerebroventricular administration of tyrosine on the blood pressure of normotensive and hypertensive rats, and on brain levels of the major catecholamines and their metabolites; and to test the effects of chronic treatment with other neutral amino acids on the development of hypertension. Studies are also under way to examine the effects of stress on sodium retention of the kidney and blood pressure control.

Data from another animal study of blood pressure in normotensive WKY and spontaneously hypertensive (SHR) rats indicate that the dose and temporal effects of tryptophan on blood pressure are not related to its effects on brain serotonin levels. L-tryptophan, unlike D-tryptophan, appears to decrease blood pressure in SHR or WKY rats; however, there is no difference between D- and L-tryptophan in their

ability to increase brain serotonin levels. These results indicate that the cardiovascular effects of L-tryptophan are not mediated by brain serotonin levels.

The effects of dietary modification on blood pressure control are being studied in mildly hypertensive patients and in young normotensive adults. The study of mildly hypertensive patients is evaluating three aspects of nutrition intervention in terms of their effects on changes in blood pressure; i.e., no dietary change, weight loss, and decreased sodium and increased potassium intake. The other study on dietary modifications and blood pressure control, under way in young adults attending boarding schools in New England, is examining the effects of variations in sodium and linoleic acid intake on blood pressure. For 1 year, the diet prepared at one school will contain 50 percent less sodium resulting in an anticipated reduction of total sodium intake by students of approximately 35 percent, to an average level of 75-90 mEq/day. The intervention will be changed to another school during the second year. During the third and fourth years, sodium intake will be kept at the usual levels, while the polyunsaturated fatty acid intake of students is doubled from 4 to 8 percent of calories alternately at each school. This study offers the opportunity to determine the frequency and magnitude of changes in blood pressure in young persons given modifications in sodium and linoleic acid intake.

Short-term human studies suggest that the hemodynamic basis of differences in sodium sensitive individuals and sodium resistant individuals appears to lie in sodium's property of decreasing vascular resistance in normal subjects, while increasing resistance in hypertensive subjects. Additional studies are needed to verify this finding and to determine its long-term significance. Noninvasive methods of estimating changes in total peripheral vascular resistance in response to dietary sodium manipulation using echocardiography and venous occlusion plethysmography will be tested as a means of identifying the salt-sensitive individual in the population who might benefit from preventive dietary measures.

Large scale clinical trials on primary prevention of hypertension are under way to assess the efficacy of different forms of dietary intervention in preventing the development of hypertension. The participants, who are at high risk by virtue of high normal diastolic blood pressures and increased relative weight, will be randomly assigned to a control treatment or to one of four dietary interventions, i.e., sodium consumption reduced to about 70 mEq/day, sodium about 70 mEq/day and potassium supplementation, caloric restriction to achieve desirable body weight, or a combination of sodium and caloric restriction. The trial includes a data coordinating center, nutrition and education resources center, a central biochemistry laboratory, and a food record coding center.

Since hypertension is a major health risk associated with obesity, it seems that weight loss therapy, combined with exercise and behavior modification, may be a practical alternative to pharmacological therapy for certain categories of obese, hypertensive patients. A



study is under way in 300 obese hypertensive men and women on the effects on blood pressure of two different outpatient dietary interventions that restrict calories (two 600 calorie diets, one with and one without carbohydrates) compared to a control diet of moderate restriction (1,500 calories). Sodium, potassium, and calcium excretion will be measured in order to examine the possible impact of salt beyond that of weight reduction alone. The association between the dietary interventions and changes in blood pressure due to weight loss will be quantified, both during active treatment and for two years of followup. The results of this research will improve the safety and effectiveness of nonpharmacological treatment of obese hypertensives, and provide data to help identify subgroups among the obese population who may be effectively treated with weight reduction programs.

## OBESEITY

In order to better understand the physiology of obese individuals and their propensity for chronic disease, studies of obesity have focused on the metabolism of adipose tissue and dietary induced thermogenesis. Specific aims are to improve the methods for the assessment of body fatness and to assess heat tolerance in the obese individual. Studies on dietary induced thermogenesis have focused on the role of brown adipose tissue (BAT) in the regulation of energy balance. The role of BAT to the overall thermic effect of consuming single meals is currently being quantified, and the effects of the macronutrient composition of the test meal on the magnitude of specific dynamic action originating from the BAT is being determined. One hypothesis being tested is that obesity which develops from a high fat or high sucrose diet results from a reduced BAT thermic response to single meals containing these nutrients. A second hypothesis is the degree to which heat production from BAT serves as a feedback signal for satiety.

Other animal studies of obesity attempt to identify the mechanisms behind the increased efficiency of energy utilization in the obese (ob/ob) mice and rats, as well as in the spontaneously obese monkey. The effects of diet and environmental temperature on sympathetic nervous system activity, as indicated by norepinephrine turnover in brown adipose tissue and selected other organs of lean and obese animals, are being examined. These data will help to identify metabolic events that permit a high retention of dietary energy in these animals and thereby increase our understanding of the metabolic basis for the development of obesity. This information is essential to developing improved nutritional approaches to the prevention and control of obesity.

Studies are also under way to determine the optimal hypocaloric diet, as well as the role of exercise and behavior modification techniques for the treatment of obesity. Low carbohydrate and low protein diets are being examined for their ability to spare body protein while maximizing fat losses. Investigators are examining various dietary regimens in preventing the relapse that often follows weight reduction in the obese. The metabolic basis of recidivism exhibited

by formerly obese patients who have lost weight is also being studied. Such research will help develop recommendations as to the optimal diet composition for the treatment of obesity.

Research under way to examine the metabolic effects of feeding behavior includes studies on the effects of changes in caloric density, especially dietary fat content, on food intake and various metabolic parameters. Such research provides information on whether the control of caloric intake is related to the metabolic consequences of the diet.

Studies are under way on the role of the hypothalamus and the autonomic nervous system in controlling food intake and metabolism in order to determine the neural mechanisms of body weight regulation and feeding. Peptides present within the central nervous system (cholecystokinin, thyroid releasing hormone, and insulin) are involved in regulating feeding behavior and, therefore, in the control of body weight. Cholecystokinin (CCK) peptides are present in the brain in high concentrations, especially in the cortex and hypothalamus. Research in sheep has shown that CCK is an extremely potent suppressor of feeding behavior when injected into the cerebral ventricles, whereas injections of CCK antiserum into the cerebrospinal fluid block satiety. Bombesin is also being studied as a potential short-term single meal satiety factor, whereas insulin is being explored as a long-term satiety factor.

Pancreatic polypeptide is known to reverse hyperphagia, obesity, hyperglycemia, and hyperinsulinemia in congenitally obese rodents, and its release is known to be caused by bombesin and cholecystokinin. Studies are under way to examine the release of pancreatic polypeptide in obese patients with Prader-Willi syndrome and to determine whether its release or synthesis is altered in these patients. A unifying theory of hormonal control may emerge if, in fact, other brain gastrointestinal peptides induce satiety through the release of pancreatic polypeptide.

A number of investigators are studying characteristics of patients involved in behavioral modification strategies for weight loss. Their goal is to develop a mathematical model that can be used to test different hypotheses concerning interactions among variables and model the sequences of causal events. It is hoped that this research leads to the development of a potentially useful method to evaluate individual differences in response to treatment for weight loss and can thus be used to predict outcome of behavioral treatment for obesity. Other studies of behavior modification strategies useful for weight loss are investigating the use of monetary contracts for promoting weight loss and weight maintenance.

The metabolic relationships of obesity and diabetes are being studied by investigators examining whether the addition of an exercise program to a regimen of dietary adjustment and weight loss increases the degree of reversal of insulin resistance, or compensates for defects of insulin secretion in overweight patients with type II noninsulin-dependent diabetes mellitus. Other studies on diabetes are consid-



ering the effects of oral fructose ingestion on serum glucose and insulin levels. It is believed that long-term fructose consumption will not result in adverse side effects and will be superior to the standard diabetic diet in maintaining the hyperglycemic control in diabetic patients. The hypothesis that reactive hypoglycemia will be attenuated following fructose ingestion is also being investigated.

## KIDNEY DISEASE

Research on the nutritional implications of kidney disease has shown that the management of kidney patients requires restriction of sodium, potassium, phosphate and fluids. Progressive loss of kidney function changes additional endocrine and metabolic functions. Nutritional therapy for the treatment of patients with chronic renal failure has important implications for reducing the frequency and perhaps the need for dialysis. Low protein diets have been shown to maintain nondialyzed chronically uremic patients relatively free of uremic symptoms. Some patients with end-stage renal disease who retain residual function have been successfully maintained with low protein diets coupled with reduced dialysis.

Research on chronic renal failure in a rat model is observing possible consequences of a high phosphate diet on the loss of kidney function. Studies are also under way to gain a better understanding of the role of the kallikrein-kinin system in the kidney by examining the direct effect of bradykinin on sodium and potassium transport in the isolated perfused rat cortical collecting duct. Data collected to date show for the first time a direct inhibitory effect of bradykinin on sodium reabsorption. Another study is examining the protective effects of dietary protein on the incidence of pathological lesions associated with severe renal hypertension in certain rat models.

## NUTRITION AND EYE DISEASE

In order to develop better therapy for the prevention and/or cure of xerophthalmia, keratomalacia, and epithelial healing problems of the eye, a number of studies are examining the role of various nutrients in maintaining the metabolic integrity of the eye. Investigators are examining corneal inflammation, ulceration, and repair in animal models in order to define specific aspects of cellular interactions and thereby determine appropriate therapeutic pharmacologic interventions. Retinoic acid, nonsteroidal anti-inflammatory agents, cholera toxin and sodium citrate are being investigated for their effects in preventing ulceration and supporting corneal repair. Studies on corneal regeneration with drugs, growth factors, and intraocular surgical procedures are also under way in order to obtain information that will lead to a better understanding of the pathogenesis of keratomalacia in vitamin A deficiency, and therefore to better therapy for its prevention and/or cure. Results of this research may also help to prevent corneal complications.

The regulation of fluxes and metabolism of vitamin A in the retina and retinal pigment epithelium is not well understood. Studies are under way on the enzymes, retinal ester esterase and synthetase, and on rhodopsin and retinol binding proteins which metabolize vitamin A in the eye and therefore could be points of regulation. The two enzymes will be purified to homogeneity and their mechanisms of action determined by an assay which investigates whether the two enzymes are regulated by light, and also quantitatively measures the retinol binding of proteins and determines whether it too is regulated by light.

Rhodopsin is the photosensitive pigment found in vertebrate rod photoreceptors which consists of the chromophore 11-cis-retinal, covalently linked to the protein opsin. A study on the physiological properties of rhodopsin, particularly those linked with the regulation of visual sensitivity, is examining the utilization of vitamin A compounds (putative precursors of 11-cis-retinal) photoreceptors during dark adaptation. In the intact eye, the regeneration of rhodopsin in the receptors relies on the supply of some form of vitamin A by the pigment epithelium. The objective of one study is to obtain evidence on the nature of this vitamin A derivative and its transformation within the vertebrate eye.

Age-related changes in the retina and retinal pigment epithelium (RPE) have been characterized by morphological and biochemical techniques. One of these has revealed that during senescence the amount of basal plasma membrane per unit RPE cell length increases substantially, the regional distribution of the basal infoldings along the RPE become irregular, and the average depth of penetration of the basal infoldings into the RPE increase dramatically. Such studies have allowed for a clearer understanding of the factors responsible for age-related retinopathies. In addition, a number of fluorophores have been extracted and separated from lipofuscin, the pigment which accumulates progressively with age. It appears that the fluorophores in the rat are remarkably similar to those found in the human RPE, suggesting that the rat may serve as a good model for studying the factors responsible for lipofuscin accumulation in the human.

Studies on senile macular degeneration (SMD) are under way to examine if selenium supplementation is an appropriate method for reducing the progress of SMD, since it appears that the degree of human SMD severity is inversely correlated with the level of glutathione peroxidase enzyme (GSH-Px), a selenium dependent enzyme. Lowering dietary selenium below a threshold level leads to a linear decline in plasma GSH-Px activity in humans.

An exciting area of nutrition and eye research involves the study of the pathogenesis of the abnormalities of diabetes using sucrose intoxication as a model of diabetes induction in nondiabetic animals. Rats are reared on 65 percent sucrose diets for 6 months of life or longer, with the resulting vascular abnormalities in the retina and kidney and changes in nerve tissue associated with the duration of feeding. For example, in rats provided sucrose as the sole source of food for 10 months of life, the most frequently observed retinal

vascular abnormality was an atrophy of capillaries with concomitant appearance of numerous collapsed vessels. Supplementation of the high sucrose diets with chromium and selenium, and increasing the lipid level of the diet prevented the vascular damage including the capillary closure. The purpose of this study is to determine in detail the scope of the damage induced by the high sucrose diets and the protection afforded by supplementation.

#### NUTRITION AND ORAL HEALTH

Studies on the nutritional factors related to oral health status are considering the effects of various nutrients such as fluoride, strontium, vitamin A, zinc, and protein, as well as the effects of overall nutritional status of individuals such as bulimics on oral health.

Investigators are considering the effectiveness of strontium and fluoride combinations in preventing caries by examining the reactions of synthetic apatite to acid in the presence of strontium and fluoride and the remineralization of artificial lesions in the presence of strontium and fluoride solutions. A study is also under way on the cost, feasibility, and effectiveness of utilizing preventive dentistry aids, such as sealants and self applied fluorides, in a 3-year school-based program to determine the maximum levels of caries prevention achievable in a school-age population.

Sodium fluoride mouthrinsing is also being examined in a double-blind clinical trial, testing its ability to prevent the development of root and coronal caries in adults who reside in a community where the drinking water contains less than 3 ppm fluoride.

Since vitamin A is essential to the proper calcification of bone and dentin, research efforts are attempting to elucidate the cellular and biochemical events that mark the nutritional influence of a vitamin A deficiency on the mineralization of bones and teeth. Data from rats deficient in vitamin A have shown that vitamin A is important in the metabolism of sulfated glycosaminoglycans, the morphologic integrity of dentin, and dental caries susceptibility.

Zinc deficiency in the rat has been shown to stimulate the activity of the lining of the epithelium in some regions of the oral cavity, especially the cheek, while inhibiting or not affecting other regions. Experiments are under way to examine further the role of zinc in the oral epithelium.

The effects of dietary lipids on the salivary gland's plasma membrane lipid composition, fluidity, enzyme activities and saliva composition are being assessed in terms of essential fatty acid deficiency, feeding of saturated versus unsaturated fats, cholesterol supplementation, and the trans fatty acids.

Studies are also under way to examine the influence of protein-calorie malnutrition on local and systemic host defense components known to influence oral health. Alterations of host defense components are being correlated with morphometric analysis of inflammatory infil-



trate of the gingiva tissue. Knowledge of changes in host defense components with varying degrees of malnutrition could form the basis of understanding the influence of protein-calorie malnutrition in oral disease.

In order to understand whether eating disorders such as bulimia are associated with oral health status, the following parameters of bulimic patients are being investigated: the incidence and severity of oral signs and symptoms, the proportion of salivary and pancreatic amylase isoenzyme activities, and the stimulated resting parotid salivary flow.

Other research on nutrition's role in the prevention of dental caries includes development of noncariogenic sweeteners which are stable and safe, and studies to investigate the role of sucrose in caries development. Since preliminary reports have indicated the noncariogenicity of peptide sweeteners, attempts are being made to develop such sweeteners through modifications of l-aspartyl-l-phenylalanine methyl ester, trifluoroacetyl-l-aspartyl-p-cyanoanilide, etc. In addition, acesulfam K is being studied for its potential use as a noncariogenic sucrose substitute since it is 300 to 350 times sweeter than sucrose and shown to have a near zero caries score when compared to sucrose and raw corn starch. Other investigations are under way to examine the transmission of S. mutans and subsequent caries incidence in rats fed different concentrations of sucrose.

#### DISEASES OF THE NERVOUS SYSTEM

Studies dealing with nutrition's role in the prevention of nervous system diseases include investigations of synthetic and plant neurotoxic agents, such as beta-N-oxalylamino-L-alanine (BOAA) found in the Lathyrus sativus or chickling pea, on the molecular and cellular mechanisms underlying neuronal development, maintenance, degeneration, and regeneration. BOAA is considered to be the neurotoxic substance responsible for human lathyrism, a condition characterized by spastic paraplegia, pain, hyperesthesia, and paresthesia. These studies allow for a comparison of experimental motor system disease with primary lateral sclerosis and related motor system diseases.

Neurological complications resembling those seen in human pernicious anemia, without the hematological complications, can be observed when cobalamin deficiency is induced in the fruit bat (Rousettus aegyptiacus). A number of studies are being carried out to compare the effects of cobalamin, methionine, and choline in preventing the neurological changes in these cobalamin deficient animals. The results of this research will elucidate the metabolic role of cobalamin in nervous tissue, as well as its interaction with other nutrients. Also, the role of lysine in the etiology of human genetic diseases, sedation, sleep, and neuronal functions related to neurological disorders is being studied in projects measuring the endogenous contents and subcellular distribution of lysine metabolites in the brain.

The neuroanatomical organization of the nervous system that controls food intake and body weight regulation is being elucidated and will help to develop possible therapeutic approaches to obesity. The relationship of spontaneous obesity to monoamine function is being investigated in studies of genetically obese mice. These studies are examining the relationship of disturbances in autonomic functions and abnormal catecholamine metabolism to feeding behavior and resulting body weight.

Other studies of the neural control of ingestive behaviors use neuro-anatomical, electrophysiological, and behavioral analyses to elucidate the neural mechanisms that govern the decision to ingest or reject the contents of the oral cavity. Results of this research will provide insight on how sensory information such as taste is used to regulate the biological behaviors of ingestion and rejection of food. One study is examining the neuroendocrine control of drinking elicited by eating and the role of endogenous histamine in this process. Another investigator is attempting to determine the relative extent to which abnormal drinking behavior around mealtime contributes to the development and/or maintenance of hypertension in animals.

Investigations on the effects of different diets on plasma amino acid pattern and neurotransmitters in the brain, particularly serotonin and catecholamines, are under way in order to gain a better understanding of feeding behaviors and of treatment of various conditions such as liver disease, genetic defects, obesity, and anorexia nervosa. Studies of amino acid metabolism are looking at alterations in the metabolism of branched chain amino acids as a result of liver failure (which appear to affect brain neurotransmitter concentrations and mental activity), trauma (in which the branched chains amino acids reduce nitrogen loss), renal disease and urea cycle diseases (in which the branched chain amino acids improve nitrogen utilization), and diabetes and long-term fasting or starvation.

#### NUTRITION AND IMMUNE FUNCTION

Studies are also under way to examine the modulating effects of trace elements such as iron and zinc on microbial virulence, the maintenance of immune function, and the prevention of infection. Iron is essential for microbial growth and the iron transport process has been linked to the pathogenicity of several microbial infections. Transport of iron occurs via several different mechanisms; microbial iron transport and mobilization is achieved by siderophores or siderochromes manufactured by the organism, as needed, in order to extract iron from the environment and concentrate it within the organism. The molecular mechanisms for iron assimilation in microorganisms are being examined through studies of the aerobactin transport system in selected strains of enteric bacteria. Another study is seeking evidence that ferrous ionophores are produced by anaerobic organisms as a means of solubilizing and transporting iron. The kinetics of iron uptake via ferrous ionophores is being determined and compared to the aerobic systems, and the specificity of the transport system will be examined.



The virulence of the marine fish pathogen Vibrio anguillarum is largely dependent upon a very efficient plasmid mediated iron sequestering system. This system enables the bacteria to proliferate in the vertebrate host body fluids and tissues in which iron is complexed to iron binding proteins like transferrin and lactoferrin and thus unavailable for bacterial use. A better understanding of the virulence associated property and iron uptake of bacteria may help to prevent many of the septicemic diseases of man.

A clinical trial is under way to determine whether the growth of Pseudomonas aeruginosa in human plasma is related to the virulence of the strains. Growth of most strains of P. aeruginosa is impeded by transferrin which withholds essential iron from the bacteria. Research is under way to elucidate the mechanisms of iron acquisition of P. aeruginosa, particularly in resistant strains which grow rapidly in human plasma.

The pathogenicity of Corynebacterium diphtheria is primarily due to the production of a potent exotoxin which inhibits cellular protein synthesis. Studies have shown that iron is the single most important factor that depresses toxin production; the exact mechanisms are under investigation.

During infection, a synergism appears to exist between the development of fever and changes in trace metal levels (e.g., plasma iron and zinc levels fall, and copper levels rise). This synergism enhances the host's defenses against infectious organisms. For example, changes in plasma concentrations of iron coupled with elevations of temperature decrease the in vitro growth rate of certain bacteria. More studies are under way to learn more about the possible synergism of plasma levels of trace metals and the role of fever in host defense responses to infection. Other investigators are examining protein and zinc deficiencies in terms of their effect on the efficacy of BCG vaccine since malnourished animals have been shown to have impaired cell mediated immune function.

Animal models of inflammatory diseases such as arthritis, diabetes, and atherosclerosis are being studied in order to determine in vivo the involvement of lipid peroxidation in the initiation and course of these diseases. In situations where lipid peroxidation is found to occur, the ameliorative effects of the dietary antioxidants, vitamin E and selenium, or injected vitamin E, are being ascertained. The biological activities of alpha and gamma tocopherol are being compared by measuring their effectiveness in inhibiting pentane production. In addition, the role of toxic compounds such as halogenated hydrocarbons, hydroperoxides, heavy metals, and carcinogens in inducing lipid peroxidation are being examined.

#### FOOD ALLERGY

Studies to better understand the mechanisms of food allergy, its diagnosis, and treatment or prevention are under way in adults and in children with atopic dermatitis. Investigators are attempting to determine if adults with recurrent idiopathic anaphylaxis and system-

ic mastocytosis are also sulfite sensitive. Other investigators are evaluating the prevalence of food allergies in children with atopic dermatitis, and the role of IgE mediated reactions to foods in its pathogenesis. Information from these studies will provide insight on the pathogenic mechanisms involved in food allergy and guidance for appropriate therapeutic measures.

The validity of the food allergy history and elimination diets are also being tested, and the therapeutic effects of aspirin and cromolyn sodium in the prevention of adverse food reactions are being examined. This research will provide more information on the opportunities for objective diagnosis of food allergy in adults, as well as on the value of therapeutic strategies other than food elimination diets in preventing food allergies.

#### OSTEOPOROSIS/BONE DISEASES

Osteoporosis is a disease in which bone mass decreases, causing bones to be more susceptible to fractures. It affects as many as half of all women in the U.S. over 45 years of age and 90 percent of all women over 75 years. Several factors that influence the quantity and quality of bone throughout life include: the level of peak bone mass, the rate of bone loss due to menopause and aging, certain systemic hormones (parathyroid hormone, and calcitonin), substances produced by the bones themselves, dietary calcium intake and other dietary parameters, intestinal and kidney function, and physical forces such as body weight and exercise that act on the bones. Many scientists believe that osteoporosis can in part be prevented by taking certain precautionary measures.

The biochemical basis of calcium absorption by the small intestine involves studies on the mechanisms of regulation by dietary calcium, vitamin D, growth, aging, and other factors. Research is under way to provide insight on the dynamic conservation of calcium in bones, since bone resorption is known to vary with age, diet, physical activity, etc. Variation in bone resorption and its effects on the contribution to blood calcium levels measured will be quantified during various dietary treatments and with age. Hormonal control of calcium metabolism is also being examined through numerous studies that attempt to elucidate the role of dietary calcium and vitamin D in the production and action of parathyroid hormone.

Investigators continue to examine the biochemical mode of action of vitamin D and its two metabolites,  $1,25(\text{OH})_2$  vitamin D and  $24,25(\text{OH})_2$  vitamin D, in calcium metabolism. Determinations are being made of vitamin D (and metabolite) mediated changes in intestinal membrane composition, organization, and topology, which may affect calcium and phosphorous translocation. Results from this research will provide insight into the pathophysiological dysfunction of the vitamin D endocrine system in osteoporosis as well as a variety of diseases such as renal osteodystrophy, sarcoidosis, and vitamin D resistant rickets.

Studies are under way using various techniques to determine if age influences the ability of the skin when exposed to sunlight to photosynthesize adequate quantities of vitamin D<sub>3</sub>, an important calcium hormone, from 7-dehydrocholesterol. 7-Dehydrocholesterol slowly converts to vitamin D<sub>3</sub> over a period of days and is then bound to a specific protein which transports it through the circulation. The influence of age on the skin stores of 7-dehydrocholesterol, the cutaneous photosynthesis of vitamin D<sub>3</sub>, serum levels of vitamin D<sub>3</sub> and its metabolites, and in vitro synthesis and metabolism of 7-dehydrocholesterol in human skin fibroblasts will be evaluated.

In order to determine the effects of exercise as a modality for stimulating bone accretion in women between the ages of 40-65 years, the period of life during which the most critical bone mineral loss occurs, a study is under way to examine bone mineral changes in women on prescribed exercise programs. Sodium fluoride and calcium therapy for postmenopausal osteoporosis is being studied in terms of its efficaciousness in reducing the incidence of vertebral fractures. Other therapeutic modalities being investigated include the use of vitamin C in osteoarthritis, which is characterized by a chronic degradation of articular cartilage in the afflicted joints; and the ability of various agents (1,25(OH)<sub>2</sub> vitamin D, 24,25(OH)<sub>2</sub> vitamin D, and fluoride) to ameliorate or treat aluminum induced osteomalacia in rats.

Total parenteral nutrition, an accepted treatment for severe malnutrition secondary to gastrointestinal disease, is often associated with the appearance of a disabling bone disease, characterized by normal or elevated serum calcium and phosphorous, normal or reduced serum parathyroid hormone, substantial hypercalciuria, and reduced serum levels of 1,25(OH)<sub>2</sub> vitamin D, with normal levels of other vitamin D metabolites. Research is under way to evaluate the mechanisms responsible for altered vitamin D metabolism and/or parathyroid hormone secretion, and the causes of the hypercalciuria. The data will provide insight on the pathogenesis, management, and prevention of the metabolic bone disease resulting from TPN, delineate factors controlling the metabolism of vitamin D and parathyroid hormone, and thereby establish the means of prevention or treatment of the disease.

#### DIETARY FIBER

Dietary fiber is under investigation for its possible effect on disease prevention, especially prevention of colon cancer. Studies are under way to determine the chemical characteristics of various fiber components, to develop the appropriate methods for measuring dietary fiber, and to evaluate the effects of different forms and sources of dietary fiber components on the digestion, absorption, and bioavailability of nutrients. The effects of representative components of dietary fiber, singly and in combination, on gastrointestinal function and microbiology, and on bioavailability of micronutrients, especially zinc, iron, vitamin B<sub>12</sub>, folacin, and other vitamins, are being studied in the rat.



Data are also being collected on the role of fibers in the development and/or alteration of intestinal bacterial metabolism by monitoring enzyme activities and metabolites associated with microbial metabolism. Test fibers include cellulose, pectin, lignin, guar gum, alginic acid, xylan, and wheat bran. Interactions between indigestible dietary plant fibers, i.e., wheat bran, pectin, and cellulose, and the secretion rate and availability of digestive enzymes, such as trypsin, chymotrypsin, lipase, pepsin, and intestinal peptidase, are being studied. Cellulose or wheat bran have been shown to decrease digestive enzyme activity in the small intestine by either dilution of the contents or by interfering with enzyme activity. However, pancreatic enzyme activity increased with ingestion of wheat bran. It is hoped that the data from these experiments will clarify principles that will be useful in evaluating the total impact of increasing the dietary fiber component of the human diet.

#### STUDIES ON AMINO ACID TRANSPORT AND METABOLISM, FATTY ACID METABOLISM, THE METABOLISM OF FOLATE AND OTHER WATER SOLUBLE VITAMINS, AND TRACE ELEMENTS

Additional research on the role of specific nutrients in disease prevention includes studies on amino acid transport and metabolism; fatty acid metabolism; the metabolism of folate and other water soluble vitamins; the trace elements such as iron, selenium and zinc; and dietary fiber. These are described, in turn, below.

Studies on the metabolism of the branched chain amino acids have revealed a pathway for the metabolism of leucine that is catabolic in bacteria and appears to be synthetic in humans. The pathway depends upon the activity of the enzyme leucine 2, 3-aminomutase, an enzyme dependent upon adenosylcobalamin as a cofactor. Other enzymes which function in the pathway are beta-leucine transaminase, coenzyme A transferase, and thiolase. The relative carbon flux through this cobalamin dependent pathway and the pathway which is independent of cobalamin greatly favors the independent pathway in brain, heart, kidney and liver. In the testis, however, the cobalamin dependent pathway accounts for over 40 percent of the carbon flux. This suggests that the metabolism of leucine may play an important role in this organ. The relationship between enzyme activity and various disease states, such as pernicious anemia and inborn errors of metabolism, are also being examined.

Cysteine and tyrosine are often deficient in total parenteral solutions yet they appear to be essential for the cirrhotic patient. Studies are under way to establish the requirements for these amino acids in the cirrhotic patient. The results from this research will enable the formulation of new feeding solutions to meet the nutritional requirements of the patient with cirrhosis, and therefore to lessen the morbidity and mortality of the cirrhotic who requires hospitalization and nutritional support.

The requirements for the omega-3 fatty acids in a primate model are being examined through monitoring of plasma lipids, erythrocytes, and skin biopsies, as well as tests of retinal function through cone and

rod electroretinograms and behavioral tests of vision and learning ability. The omega-3 fatty acids are an important component of membrane lipids, particularly the retina and cerebral cortex, and are therefore important for the function of neuronal and photoreceptor membranes.

Studies are under way to characterize fat absorption and digestion vis-a-vis lingual lipase and a bile salt stimulated lipase from the pancreas. The route of absorption of the medium chain fatty acids will be considered in vivo as a function of the position of the triglyceride.

The effect of alcoholism on folate metabolism is being studied in primate models with measurements of hepatic metabolism, biliary excretion and intestinal absorption of labeled folates. Studies are also under way which consider the renal handling of ascorbic acid, pantothenic acid, and nicotinic acid as well as to elucidate the metabolism and function of the fat soluble vitamins.

Investigations are under way on the biochemistry and physiology of iron in order to synthesize efficacious iron supplements for specific therapeutic and prophylactic application. The role of copper in the absorption, storage, and utilization of iron is being examined along with the development of potential tests of iron and copper assimilation. Projects to develop a new vehicle for delivering supplemental iron and copper to anemic populations are considering the nutritional and technological consequences of fortifying milk.

The interrelationship between cobalt and iron metabolism is also being studied in order to understand better whether cobalt can be used as a probe for iron metabolism and absorption, and therefore to develop new tests for measuring the nutritional efficacy of trace elements in a variety of applications.

Other studies are under way on the effects of commonly used industrial products or byproducts, the polyhalogenated aromatic hydrocarbons, on iron absorption and other intestinal mechanisms since preliminary data show that a single dose of these compounds stimulate iron absorption and metabolism in rats. This research will also provide some information on the potential of these substances as carcinogens, mutagens and teratogens. The effects of endotoxins on alterations of zinc and copper metabolism in the liver and extrahepatic tissues are also being examined.

Since lead and mercury are common environmental pollutants, the action of these metals on kidney function is being examined in rabbits. Other studies are under way on the effects of chronic administration of lead on the absorptive function of the gastrointestinal tract. The uptake of heavy metals, such as cadmium, lead, zinc, mercury, copper and nickel, from the perfused lumen of the jejunum and their accumulation in the jejunum is being studied in terms of the influence of dietary constituents and maturation of the intestine.



Evaluating the synthesis of the zinc binding protein metallothionein as it relates to mammalian zinc metabolism involves studies on the integration of the induction of the protein to zinc absorption by the small intestine, and the regulation of plasma zinc concentration and intracellular zinc metabolism in liver, kidney, intestine, and prostate. Studies have shown that metallothionein is induced by dietary and parenteral zinc as well as the glucocorticoids.

Investigators are attempting to elucidate the biochemical mechanisms by which the chlorinated dibenzo-p-dioxins (e.g., 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD) and related compounds) produce toxicity in animals, and to determine whether altered absorption or utilization of nutrients from the gastrointestinal tract is the main contributor to weight loss and subsequent lethality in TCDD treated animals.

Due to the nature of the research described in this area of Nutrition and Prevention of Disease, many of the projects are also described under the categories of Research on Nutritional Status Assessment and Epidemiological Research on Nutrition, appendices E and F respectively.

## APPENDIX E

### RESEARCH ON THE ASSESSMENT OF NUTRITIONAL STATUS



## RESEARCH ON THE ASSESSMENT OF NUTRITIONAL STATUS

Research on nutritional status assessment includes investigations to develop and evaluate various kinds of methods useful to determining whether the requirements for essential nutrients are being met throughout the life cycle from fetal life to infancy, childhood, adolescence, adulthood and the aged. Studies are carried out in both normal and patient populations and examine: 1) biochemical, anthropometric, maturational and functional indices of nutritional status; 2) micromethods employing the latest technology and the smallest amounts to measure nutrient concentrations in various tissues and plasma; and 3) methods that improve the accuracy of dietary recall data. The NIH is the major agency that supports research for the development of methods used in nutrition surveys.

In FY 1984, NCI, NHLBI, NIADDK, NIAID, NICHD, NIDR, NIGMS and DRR supported research on nutritional status assessment in the amount of \$35 million or 18 percent of total nutrition research.

Reliable methods for the assessment of nutritional status are needed in order to: 1) determine whether or not impairment of health is the result of inadequate or inappropriate diet; 2) establish the specific nature of any nutritional problem underlying such health impairment; 3) provide knowledge on which to base dietary treatments for improving health; and 4) permit evaluation of the effectiveness of nutrition treatments or interventions that may be undertaken to improve health.

### FETAL AND INFANT NUTRITION

The nutritional status of the mother prior to and during pregnancy is but one of the many important factors that influence fetal growth and thus, birth weight. Genetic factors, infections, placental abnormalities, toxins, the working environment, maternal obesity, diabetes, hypertension, toxemia, alcohol intake, and smoking in pregnancy are known to influence birth weight and hence fetal outcome. Interference with the delivery of the nutrients to the fetus or the inability of the fetus to adapt to the physiological changes that occur during pregnancy because of congenital defects or chromosomal abnormalities usually result in overt fetal malnutrition. Attempts to determine specific nutritional demands of the fetus and to uncover the possible role of nutrition before and immediately after birth in modulating growth and development has led to explorations of the environment of the fetus and the neonate.

One-third of all infants born weighing less than 2,500 grams are full-term infants whose growth has been retarded in utero. Intra-uterine growth retardation is associated with an increased incidence of intrapartum asphyxia, neonatal morbidity, neurological abnormalities, and decreased brain cellularity. Such growth retardation appears to be caused by an inadequate flow of nutrients and oxygen across the placenta from the mother to the fetus. The metabolic alterations and changes in umbilical uptake of nutrients and oxygen

that occur as growth retardation develops are unclear and are under investigation.

One study is evaluating the effects of long-term supplemental nutritional therapy on sheep fetuses growth retarded because of maternal malnutrition resulting from either restriction of protein and calories to the mother or microinfraction of the placenta, and on normal control fetuses. A balance of amino acids, glucose, and acetate is being infused continuously over the last month of gestation as either intragastric supplements, amniotic supplements, or umbilical venous supplements. Fetal length and weight; hind limb length; maternal weight; metabolite levels in fetal blood, maternal blood, and amniotic fluid; nutrient delivery to fetal organs; and the umbilical uptake of nutrients are being measured.

Studies of dietary deficiency and ethanol intake during pregnancy on neural development are being carried out in rats by using a two factor model which considers the effects on the fetus of one mild dose of ethanol given to well fed dams versus the same dose given to zinc deficient dams. The study design includes determining if critical periods exist during which such brief treatments are particularly harmful to the offspring. The morphometry, morphology and function of the hippocampal region of the brain following this treatment are being assessed using neuroanatomical and behavioral methods. Other studies under way in animals are examining the possible role of zinc in the fetal alcohol syndrome.

Multiple studies conducted throughout the world, including Western populations, have indicated that marginal levels of zinc deprivation may in fact exist in human populations and that zinc deficiency may occur as a result of either inadequate zinc in the diet, or as a result of multiple factors including pregnancy. Studies on the effects of a marginal zinc deficient diet given to pregnant Macaca mulatta monkeys have shown that even when begun after conception such a diet has marked influences on the nutritional status, anthropometric parameters, immunological function, and behavior of newborn animals. Investigators plan to study these effects of marginal zinc deficiency, along with the teratogenic influences of long-term marginal zinc deficiency begun 1 year prior to pregnancy, on the newborn. The reversibility of these effects is also being examined.

A number of studies are under way to determine incidence, etiology, clinical and laboratory features, and the optimal means of detection and effects of treatment of human zinc deficiency in pregnant women, infants and children. Appropriate diagnostic criteria for marginal zinc deficiency have not been determined; i.e., the site of zinc absorption and homeostatic control mechanisms in the gastrointestinal tract during zinc deficiency and sufficiency are not well characterized in human subjects. Studies are under way to develop in vitro assessments of lymphocyte functional activity as a measure of zinc status and to examine appropriate measures of gastrointestinal absorption, zinc balance, and endogenous secretion of zinc. These studies will help to provide sensitive criteria for the diagnosis of a marginal zinc deficiency and provide more insight on the homeostat-



ic control mechanisms of zinc at the level of the gastrointestinal tract.

Additional procedures being tested for their potential role in improving the assessment of zinc status include determinations of zinc in plasma, hair, urine, and parotid and mixed saliva; the effects of topical zinc on delayed hypersensitivity; plasma zinc response to pharmacological doses of oral zinc; stable zinc isotope studies; gel chromatography and mass spectrometry analysis of zinc containing fractions from human milk and duodenal juice. Use of saliva as a diagnostic tool for mild zinc deficiency is receiving research attention in terms of whether collection, storage, and analytical procedures have an effect on salivary zinc concentrations. One objective of this research is to determine the reproducibility of salivary zinc levels in the same individual with repeated determinations under variable (free living) and identical (controlled) diets. These studies should indicate the reliability of saliva as an additional assessment tool for evaluating mineral status.

Studies of pregnant animals have shown that a metabolic interaction occurs between cadmium and zinc which may result in the fetus receiving less zinc. One study under way is testing the hypothesis that the increased cadmium level in pregnant women who smoke alters the metabolism of zinc by the maternal-fetal placental unit, which may contribute to low birth weight infants. Cadmium levels in pregnant women who smoke have been shown to be 56 percent higher in whole blood and 32 percent higher in placental tissue. In order to evaluate whether cadmium exposure due to smoking affects zinc metabolism, various biochemical and clinical parameters of smokers and nonsmokers are being compared. Zinc status of the mothers and infants are being evaluated using plasma and red cell zinc levels, and serum alkaline phosphatase activity. The levels of zinc and alkaline phosphatase are also being measured in the placenta. Cadmium exposure is being evaluated by determining the levels of cadmium in maternal blood and placental tissue, and by determining metallothionein levels in the placenta. This study will provide insight concerning the interaction of cadmium with zinc during pregnancy, and may provide evidence that cadmium exposure through cigarette smoking contributes to lower infant birth weight.

The nutritional status of the mother during pregnancy is also being examined for its effects on brain development of the newborn and the occurrence of mental retardation syndromes, neonatal lymphocyte function, etc. Protein restriction during pregnancy is being studied for its effects on brain development and subsequent behavior in rats whose mothers were protein malnourished for 5 weeks prior to mating and then maintained on a low protein diet throughout pregnancy and lactation. Anatomical, physiological, biochemical, and behavioral studies are being carried out; learning, memory, and motor development are being examined in behavioral experiments.

Investigators are studying biochemical techniques to delineate cellular abnormalities responsible for mental retardation syndromes. The roles of the trace metals, especially copper, zinc and chromium in

conjunction with maternal undernutrition and environmental deprivation are being examined in terms of brain development and mental retardation.

In order to gain a better understanding of the effects of intra-uterine malnutrition on neonatal lymphocyte function and its correlation with risk of neonatal infection, studies are under way on lymphocyte mitogen-induced proliferation and class specific immunoglobulin biosynthesis following in utero malnutrition, and the correlation between these responses and the development of neonatal infection. The effects of blood glucose levels on gluconeogenesis in both the diabetic mother and her newborn; the effects of hyperinsulinemia in fetal monkeys on metabolic and hormonal changes; and the effects of hypoglycemia in neonates on behavioral changes, etc.

It is essential that the infant, especially the premature or low birth weight infant be provided with adequate amounts of essential nutrients to meet nutrient requirements during the neonatal period. The continued growth and development of the neonate is totally dependent on the maintenance of nutritive support. The factors that influence the delivery of proper nourishment to the infant include the nutritional status of the mother during lactation, the availability of nutrients from the various feeding formulas, etc. Studies are under way to examine these factors in order to better define the nutrient requirements of neonates, and the ability of various feeding regimens to meet these requirements and thereby influence the subsequent growth and development of the infant.

The mechanisms by which protein-calorie malnutrition of the mother affects lactation are being examined in the rat. Six hypotheses being tested are: 1) malnutrition has a significant effect on levels of hormones known to be important for galactopoiesis in the rat; 2) malnutrition has a significant negative effect on the normal lactational hypertrophy of the mammary glands, liver, and gastrointestinal tract; 3) malnutrition has a significant negative effect on cardiac output and blood flow to the mammary glands; 4) beyond any effect of reduced blood flow, there is little additional effect of malnutrition on nutrient uptake by the mammary glands; 5) previously malnourished animals refed during lactation do not differ significantly from controls; and 6) chronically malnourished rats respond to their dietary treatment significantly different than those first underfed during lactation.

Vitamin A metabolism and status in neonatal life is also being studied. In one experiment, pregnant ewes are being fed four different doses of retinol during their pregnancy. The offspring neonatal lambs are then given colostrum containing labeled vitamin A obtained from the ewes fed the four vitamin levels in order to examine vitamin A transport into colostrum, as well as neonatal absorption and metabolism of vitamin A. The effects of varying protein intakes during pregnancy on placental transport of vitamin A, and on tissue and fluid levels of vitamin A are also being considered. It is known that placental transport and fetal metabolism of vitamin A are responsive to maternal vitamin intakes, and that maternal vitamin A

intake alters colostrum and milk levels of vitamin A. Results from this research will provide more information on the roles of protein and vitamin A in retinol metabolism during pregnancy and in the neonate.

Investigations in mammals are analyzing the hormonal control of calcium metabolism during lactation and postnatal development. These studies focus on the role of vitamin D and the endocrine system on calcium metabolism. Interactions of vitamin D with parathyroid hormone and calcitonin during lactation and the newborn period are being investigated. This research attempts to elucidate factors involved in the pathogenesis of neonatal hypocalcemia, rickets and osteopenia.

A number of studies are examining the effects of different infant feeding practices on the nutritional status of premature as well as normal term infants through the use of various biochemical, clinical, and anthropometric indices. The bioavailability of a number of vitamins and trace elements and the utilization of protein and energy from various feeding regimens is being assessed; the use of fat emulsions to nourish the low birth weight infant is being examined; and the ability of breast milk to supply the premature and full-term infant with essential nutrients is being investigated in studies of human milk banking.

Folate status of infants is usually in a delicate balance, particularly in low birth weight infants. Recent clinical studies suggest that breast feeding affords considerable protection against folate deficiency in infancy, and that breast milk contains a very high molecular weight binder for milk proteins which enhances folate availability for uptake by intestinal cells. The quantity and quality of the folate binder in milk obtained at different times in the lactation period from various mothers will be assessed, along with the enhancement of folate uptake in the infant. The effects of gestational age and maternal age will also be considered.

Investigations on the vitamin D status of breast-fed and formula-fed neonates include studies to define the antirachitic sterol requirements of preterm and term infants. Various doses of vitamin D, 25-OH-D, and 1,25-OH<sub>2</sub>-D are being examined in terms of vitamin D metabolites and calcium balance. This data will provide insight into the vitamin D metabolism of the neonate, the supply of antirachitic sterols in breast milk, the amount and types of vitamin D metabolites required by the neonate at various gestational ages, and thus may help to define more precisely the vitamin D requirements of the low birth weight and/or premature neonate.

The bioavailability of dietary calcium, zinc, and copper is being measured in premature infants fed either a proprietary formula, their own mother's milk, or their own mother's milk fortified with a mineral supplement. This study is examining the accuracy of the stable isotope enrichment technique (i.e., use of nonradioactive naturally occurring isotopes, <sup>70</sup>Zn, and <sup>65</sup>Cu) for determining bioavailability. Isotopic and mineral analyses of urine and stool



samples will permit an accurate calculation of the fractional absorption of each administered stable isotope. This study will compare the bioavailability of dietary calcium, zinc, and copper from the various feeding regimens, while also determining the effect of post-natal age on availability of these elements.

In order to better define the precise interrelationships of selenium, iron, folate, tocopherol, and vitamin B<sub>12</sub> on the hematological status of the premature infant, various feeding regimens that provide supplemental folate, supplemental B<sub>12</sub> or a combination of both, are being examined for their relationship to the maintenance of optimal hematopoietic development. Micromethods are used to assess weekly blood counts and plasma levels of vitamin E, selenium, iron, folate, and B<sub>12</sub> (bound and total), as well as red cell selenium and glutathione peroxidase. Data on levels of transport proteins, and maternal nutritional, hematopoietic, and serological status are also being collected. This research will help to develop guidelines for optimal hematopoietic development of the premature infant.

Studies of selenium intake of infants have shown that approximately 60 percent of infants fed human milk, and 95 percent of the formula fed infants have selenium intakes below the recommended 10-40 micrograms/day. Human and animal studies are under way to characterize the chemical forms and distribution of selenium in human milk; determine the influence of supplemental dietary selenium on human milk; determine the relationship between blood and human milk selenium fractions; and determine the relative efficacy of supplemental dietary selenium as sodium selenite, selenocysteine, selenomethionine, and selenium enriched yeast on human milk content. The influence of maternal selenium supplementation provided during lactation on the infant's selenium status is being examined, and the relative bioavailability of human milk selenium is being determined using an animal bioassay.

High pressure liquid chromatography, ion chromatography, and mass spectrometry are being used to analyze the content and distribution of individual selenium containing compounds. Studies will also be conducted to determine the influence of form and quantity of dietary selenium on milk selenium content and distribution. Differences in the content and/or distribution of selenium will then be evaluated for their effect on selenium bioavailability.

The question of appropriate protein intake of the low birth weight infant is being considered through studies that examine human milk versus artificial formula as an appropriate source. The effects of these two feeding regimens are being investigated in terms of immunological development of the infant, differences in body composition, and energy expenditure. Intravenously administered amino acids are also being studied in an effort to design a mixture of amino acids which will result in a normal plasma amino acid pattern.

Another method of feeding the low birth weight infant uses the intravenous fat emulsions to provide sufficient calories to the infant, while limiting glucose and amino acids to well tolerated amounts.

Studies are under way in order to determine the optimal means of administration of these fat emulsions (which produce the least changes in lipid plasma patterns). Three methods of administration being studied in terms of their effects on plasma lipid and bilirubin levels are: the administration of fat emulsions continuously over 24 hours in progressively increasing dosages; infusion over shorter periods of time with a rest of several hours in between; and infusion without progressive increase in dose.

Investigators have shown that infants fed commercial formula which contains little or no taurine have reduced plasma taurine levels when compared to similar infants fed human milk. Also, retinal damage associated with taurine deficiency has been documented in human infants and children. A preliminary study of infant rhesus monkeys raised on a human infant protein hydrolysate formula provided data which showed that decreases in plasma taurine were similar to those observed in human infants. Studies are under way to examine the effects of feeding infant rhesus monkeys with a human infant soy protein formula with and without taurine supplementation. Blood will be sampled periodically for amino acid analysis; electroretinograms and visual evoked potentials will be recorded at three monthly intervals; visual acuity will be measured behaviorally; and animals will be sacrificed at 3, 6, and 12 months for examination of the amino acid content of tissues and the ultrastructure of retina and brain. Another group of monkeys fed the formula alone for 3 or 6 months will then be supplemented with taurine for 6 months and examined for the degree of reversibility of physiological changes with supplementation. The results of this study should provide important data regarding the requirement for taurine, and lend some insight as to the amounts of taurine which might be added to human infant formulas.

The ability of the infant to digest and utilize protein and energy from solid foods, such as oats, is under investigation in a study which is analyzing the different effects of providing 22 to 66 percent of the infant's calories from oats. For example, the absorption of trace minerals (zinc, iron, magnesium, calcium, phosphate, and possibly manganese, chromium and others) are being studied during prolonged periods of oat feeding at the highest levels of calories. The ability of wheat-legume and rice-legume mixtures to satisfy the protein needs of infants, as well as their effects on mineral absorption are also being studied. Protein requirements of convalescent malnourished infants (6-11 months) and small children (12-33 months) are being assessed with a whey/casein formula providing protein at different percentages of total calories. The adequacy of these mixtures is being judged by anthropometry, standard biochemical indices, and other measures of body composition.

The relationship between infant feeding (human milk, cow's milk, or commercial formula) and serum cholesterol levels of U. S. children ages 4-11 years is under investigation. Multivariate techniques are being used to relate current age, diet, weight, sex, race, parental income and education, and age of introduction of solid foods, and the type and duration of infant milk feeding to childhood serum cholesterol levels. Findings from this study will help identify early dietary determinants of childhood serum cholesterol levels.



Various projects on human milk banking are designed to understand better the role of breast milk in supplying nutrition to both full-term and premature infants and the physiological basis of changes in milk composition that occur during the course of human lactation. In order to identify specific maternal variables that may influence the composition and/or volume of human colostrum and milk, a dietary intake survey questionnaire is being developed; the composition of preterm human milk is being defined as a function of the length of gestation and the duration of lactation; and the effects of maternal glucocorticoid and/or  $\beta$ -adrenergic agonist therapy on the immunological properties of preterm human milk are being defined. One investigator is conducting a detailed analysis of the lipid fraction of 300 human milk samples. Data are being collected on the amount of total solids, nitrogen, nonprotein nitrogen, total lipids, triglycerides, cholesterol, cholesterol esters, phosphatidyl choline, and sphingomyelin. Fatty acid composition of total lipid and of individual lipid classes will be determined. These data will be compared to dietary intake.

Other investigators are attempting to purify and characterize growth factors in both human milk and bovine colostrum that stimulate DNA synthesis and cell division. Human milk is known to contain at least three growth factors, one of which is structurally similar to epidermal growth factor (EGF), while bovine colostrum has at least one growth factor which appears to be structurally different from EGF. The long range goals of this research are to determine the physiological role of milk derived growth factors and to use the purified growth factors for the stimulation of growth of specific cell types *in vivo*. The biochemical analysis of the structure and function of biologically active growth-promoting polypeptides will help to elucidate the physiological role of milk in the growth and development of the newborn.

The ability of the newborn to digest, absorb, and utilize nutrients is being examined through studies on carbohydrate metabolism of neonates, on the effects of vitamin E supplements on immunological status, on the various aspects of iron deficiency anemia during infancy and the role of iron supplements, and on genetic metabolic diseases of transport during infancy.

Studies on carbohydrate metabolism of the newborn have shown that extensive metabolic adjustments are required in order to maintain glucose equilibrium. One investigator is evaluating the role of glucose production in the developmental maturation of neonatal carbohydrate homeostasis using a double labeled method of deuterated glucose and  $^{13}\text{C}$ -labeled lactate.

In order to quantify carbohydrate absorption in neonates with cystic fibrosis, a noninvasive, highly specific, and sensitive breath analysis technique is being used, along with *in vitro* fecal incubations which model *in vivo* colonic bacterial metabolism of carbohydrates. This method is also being utilized to determine the effect of chronic oral antibiotic therapy on the metabolism of malabsorbed dietary and endogenous carbohydrates in the intestine, and to determine whether small bowel bacterial overgrowth is present in cystic fibrosis.

A study of the clinical and immunological status of premature infants given supplemental vitamin E is under way based on recent evidence that vitamin E may impair the capacity of the granulocytes to kill ingested bacteria. Vitamin E has been used to prevent hemolytic anemia of prematurity and has been shown to be beneficial in the treatment of retrolental fibroplasia and bronchopulmonary dysplasia. A number of immunological tests will be administered in order to establish whether currently used doses of vitamin E are beneficial or detrimental to the infant.

Iron deficiency anemia during infancy is often accompanied by muscle weakness, immunological changes, and changes in cold adaptation, behavior abnormalities, etc. Studies are under way in order to determine the molecular basis for the effects of iron deficiency on metabolism of muscle, brown fat, and brain as well as its effects on white blood cells and immune function.

The effects of iron therapy on developmental deficits and behavioral abnormalities associated with iron deficiency anemia in infants are being examined in order to determine the level of iron depletion at which infant behavior is adversely affected; to determine if injectable and oral iron supplements have different effects on behavior; to determine if iron therapy can correct the deficits; and to confirm the specific pattern of behavioral disturbances observed in iron deficient anemic infants. The results of this research may demonstrate a specific pattern of abnormal behavior and developmental test performance in iron deficient anemic infants.

Iron supplements are also being examined in terms of possible interactions of iron with copper and zinc. The nutritional status of healthy 1-year-old infants given iron supplements for 3 months is being assessed with anthropometric measurements and levels of trace elements are being determined. This research will provide some insight as to whether iron supplements alone jeopardize zinc and copper utilization by the infant and whether iron given with zinc and copper supplements is better for the infant than just iron alone will also be examined. Parallel experiments will be carried out in the rat in order to examine any mineral interactions and their physiological significance.

In order to understand the inherited metabolic diseases of infancy called the "disorders of transport," a number of biochemical techniques are being used to delineate the basic derangements of cellular function which result from the genetic abnormality phenotypically expressed as aminoaciduria, melituria, and uricosuria. Various model systems ranging from the intact animals to isolated membranes are employed in these studies.

Research on the role of the restricted phenylalanine diet on mental retardation of children suffering from phenylketonuria has been under way since 1967 in the Collaborative Study of Children Treated for Phenylketonuria of 216 children. The current investigation is comparing children remaining on the diet after 10 years with those who terminated therapy at 6 years of age to determine if PKU children at

12 years of age differ in their IQ, self esteem, behavior, and school achievement, or in their physical, neurological, or growth parameters as a function of the discontinuation of the phenylalanine restricted diet.

#### NUTRITION DURING EARLY CHILDHOOD

The dietary habits and nutrient intake of children affects their growth and development, both physically and psychologically, and may also impact on the development of chronic diseases and conditions later in life. The various factors that influence the nutritional status of infants and children include the effects of socioeconomic variables, cultural beliefs, etc., on diet.

International studies are under way to assess the specific effects of such factors on the health and nutritional status of children living in New Guinea, Colombia, and Kenya. One investigator studying the health and nutritional status of children living in the Louisiade Archipelago of Papua, New Guinea, is collecting information on the diet of various age groups, seasonal variations in food intake, time devoted to various economic activities, cultural beliefs affecting diet, food exchange, effects of feasts on production and consumption, and the demography of illness.

Studies are under way in Colombia to examine the effects of malnutrition and environmental deprivation on child development, as well as to determine to what extent it is possible to prevent retardation of physical and psychological growth by food supplementation and maternal tutoring of the children. These intervention field studies were conducted in the poor neighborhoods of Bogota, Colombia, from 1973 to early 1981. Subjects were observed longitudinally for the duration of the intervention and for 3 years thereafter through repeated measures of nutritional status assessment, intellectual functioning, and a number of concomitant social and health variables. Results of these investigations indicate that supplementation had significant effects on birth weight, physical growth, maturation, and locomotor development while early maternal psychological stimulation affected cognitive performance and enhanced growth. Continued analyses of this cohort will consider the affects of intervention on cognitive, social and behavioral development of the children at 3 and 6 years of age; and on diarrheal disease and the utilization of weaning foods during the first year of life. Subsets of the population particularly responsive to interventions will be identified, along with group variations in developmental antecedent-consequence relationships.

The multifactorial etiology of protein-calorie malnutrition of young children in the rural area of the Coast Province of Kenya is being examined. Data on specific socioeconomic factors implicated in protein-calorie malnutrition are being collected from a sample of 180 households. Variables to be studied include farming methods, household structures, land availability and command of labor supply, and sources of household income. Examples of the methods to be employed include anthropometric and clinical assessment of young children, dietary surveys, labor-time allocation studies. In addition to this



fieldwork study, similar dietary and socioeconomic data collected from over 300 households during an earlier 16-month research period are being analyzed. The results of this research will contribute to the understanding of the impact of economic development and change on the health and growth of young children, and will assist health officials in dealing effectively with nutrition problems at both the local and national levels.

In the United States, the problem of infant and childhood obesity is of major concern. A number of developmental studies to clarify factors related to the development of obesity in infants and children are under way. Patterns of eating behavior in infants and children and how these patterns relate to indices of obesity are being examined, along with how other variables such as exertion of the infants during feeding and other infant activity relate to the amount of food consumed. In addition, maternal activities during bottle feeding are being assessed in terms of their possible relationship to food consumption by the infant and the later development of obesity.

A newly discovered gastrointestinal hormone, pancreatic polypeptide (PP) has been found to be related to appetite and weight control. Recent studies have shown that children with obesity and hyperphagia associated with Prader-Willi syndrome do not secrete PP in response to a meal as do normal controls. Additional work is under way in order to compare the PP response in obese but otherwise normal children with normal children, and to investigate PP release in patients with other forms of altered appetite such as adolescents with anorexia and bulimia. The levels of PP will be correlated with the patient's nutritional status, free fatty acid levels, and other hormones shown to be altered in adults with obesity or to be important in appetite control.

Data indicate that children who experience early heart failure and hypoxia due to congenital heart disease have sparse body fat, i.e., adipose hypocellularity is evident in children with cyanotic congenital heart disease and early hypoxia, as well as in those with acyanotic congenital heart disease with early heart failure, unless these conditions are improved surgically early in life. This observation is undergoing further study. The results of this research will provide more information on the effects of hypoxia, heart failure, and palliative and reparative cardiac surgery on the body composition of children.

A longitudinal study is under way to investigate the variation of fat and fat-free body composition in children as a function of maturity, sex and racial background so that a more accurate estimate of body fatness can be developed for such methods as densitometry, hydro-metry, <sup>40</sup>K spectrometry, and anthropometry. Cross sectional studies have established that children have a lower density of fat free body mass than adults, and therefore, body fatness is overestimated in children when adult equations are used to estimate their body composition. Children with obesity or with a history of high physical activity are also being studied for their variation in fat free body composition and compared to the cross sectional data base. Methods

to measure the fat free body in all subjects include total body water using deuterium oxide dilution, bone mineral content of the cross section of the radius and ulna by photon absorption, body potassium by whole body  $^{40}\text{K}$  spectrometry, body density by underwater weighing and functional residual lung volume, and anthropometry. The relationship between anthropometry and body density will also be studied by obtaining data from several laboratories throughout the country. Thus, this research will contribute to improved body composition estimates in children for both research and clinical applications.

The relationship of sugar consumption (sucrose and corn sweeteners) to behavior, learning, and psychological function of young children is also being investigated using 7-day food records to determine intake of sucrose, other mono- and disaccharides, total carbohydrates, protein and calories. Nutrient intake of the children is being correlated to behavioral ratings of adjustment and activity levels, and to attention-task performance. The child's body weight, family size, socioeconomic status, etc., will be controlled in the analysis.

#### ADOLESCENT NUTRITION

Adolescence is the stage of profound physiological and psychological changes. The adolescent is faced not only with physical changes that are beyond his/her control, but also with psychological questions and emotional needs that society attempts to meet in various ways. Therefore, studies to determine the factors that influence dietary habits of the adolescent must consider environmental factors, such as peer pressure and fear of rejection, that may affect food choices made during this period of life.

Nutrition is one of the most important external factors that influence the physical changes that constitute puberty. The nutritional requirements of adolescence are conditioned primarily by the "pubertal growth spurt" since the growth rate during adolescence is greater than any other time of postnatal life except for the first year of life. It seems clear that the changes of puberty are hormonally determined, however, the signal for the initiation of puberty remains controversial. The nutritional status of the child prior to puberty is one factor under consideration since undernutrition during childhood is known to delay sexual development and slow growth and maturation. The mechanisms by which this occurs are not clear and are being investigated in animal models. In addition, studies are under way to examine changes in body composition during adolescence between the sexes since they appear to differ significantly, i.e., girls deposit relatively more body fat and boys more lean tissue.

The psychology of the development of food choice in adolescents and its effects on nutritional status is being assessed in 400 adolescents through the collection of five types of data: 1) cognitive development and personality data; 2) height, weight, and skinfold measures; self-perception of body weight; and social class, race and



ethnicity; 3) decisionmaking processes; 4) rating of foods in terms of possible criteria for food choice; and 5) telephone calls to obtain repeated measure of foods eaten in the previous 24-hour period. The results of this research are particularly significant since adolescent eating behavior tends to persist into adult life, and long-term consequences of eating behaviors begun early in life may impact upon the development of diseases such as heart disease, cancer, diabetes, and hypertension.

Factors such as body weight and body composition, metabolic rate, and nutritional status are related to pubertal maturation. Studies of the Macaca fascicularis monkey are under way in order to consider how the body's metabolic control systems interact with its reproductive status. The thesis that substrate limiting pathways of brain metabolism act to control luteinizing hormone-releasing hormone and gonadotropin secretion is being examined in order to identify neuroanatomical substrates which may occur as a function of pubertal brain maturation. Other studies indicate that delayed puberty associated with reduced food intake results from a negative feedback system to estrogen.

In order to identify and characterize the factors that mediate seasonal cycles in reproduction and energy balance and to elaborate the neural substrates that generate circadian rhythms in behavior and physiology of mammals, the meadow vole and Syrian hamster are being studied. Changes in body weight, food intake, locomotor activity, testosterone levels in plasma, and several other indices of reproductive status or energy balance are being measured. The findings of this research will help to develop a better understanding for the manipulation of human circadian rhythms, as well as the control of food intake and body mass. A similar experiment is being conducted in wild mice which is attempting to characterize the partitioning of energy between growth and reproductive development. The way in which young female mice apportion available calories into somatic growth, fat deposition, reproduction, and physical activity is being characterized when the costs of thermoregulation and foraging are experimentally varied in a natural manner.

The relationship of energy expenditure to the pathogenesis of obesity in adolescents is being examined in terms of resting metabolic rate, daily energy expenditure, and the thermogenic and hormonal response to overfeeding. One study is comparing daily energy expenditure in 30 obese adolescents with that of 30 nonobese adolescents matched for sex and age using the double labeled water method to measure carbon dioxide production. Anthropometric measurements will be compared to measurements of body composition in order to determine the best anthropometrical indices of body fat and lean body mass.

Another study using double labeled water is examining mean daily energy expenditure in obese and nonobese adolescents overfed by 1,500 calories, predominantly in the form of carbohydrate. Changes in resting metabolic rate and the thermogenic response to the meal containing surfeit calories will be measured at four different intervals. Changes in body composition measurements and comparisons of

these aspects of energy expenditure will help to clarify whether obese adolescents are capable of dissipating excess carbohydrate calories in a manner comparable to the nonobese adolescent.

The nutritional status of adolescent males in terms of the relationship of adiposity and sex hormones to plasma levels of lipids, lipoproteins, and apolipoproteins is being studied in a biracial population of normal students and offspring of parents with premature coronary artery disease, myocardial infarction, and/or coronary bypass surgery.

## ADULT NUTRITION

In order to gain more insight on the role of nutritional status on reproductive performance, 6,000 Dutch women who were at various stages of development during the famine of 1944-1945 in Holland are being studied. Other studies on the role of nutritional status in reproductive function are also under way in primates and mammals. The first pregnancy and resultant lactation typically occur in female primates prior to the completion of the growth phase. This additional stress may affect continued growth and subsequent reproductive capacity. Pregnancy and lactation increase the nutritional requirements of the female, and produce specific changes in the neuroendocrine system controlling ovulation; two effects which may be exacerbated in young, sexually mature females.

Longitudinal studies of four groups of rhesus monkeys are under way to determine the effects of age, parity, and maternal nutritional status on the duration and characteristics of postpartum infertility. Body weight, percent body fat, and skeletal growth will be measured in order to determine how age at first pregnancy and lactation differentially influence the completion of the growth process. A number of analyses will elucidate how the duration of postpartum infertility in primiparous mothers is influenced by the interaction of age and parity. The alterations in maternal nutritional status and basal insulin levels, etc., that characterize the first lactation will be related to the subsequent reproductive ability of the female. This project will further define how pregnancy and lactation influence the completion of growth and the parameters of subsequent reproductive activity in young primate mothers.

The effects of nutrition on gonadotropin secretion are being examined in both fasted and protein-supplemented fasted adult men and women. Ten-day fasts are being imposed upon the follicular, midcycle, and luteal phases of the menstrual cycles in women in order to determine whether any of these periods are more vulnerable to hormonal disruption by nutritional means, and whether any such disruption is sufficient to result in menstrual abnormalities (amenorrhea, corpus luteum insufficiency, or spotting). Should such disturbances be found, carbohydrate or protein supplementation will be examined as a means to prevent them. The fasting studies also consider changes in stress hormones known to affect gonadotropin secretion; stress or weight loss can also affect the biosynthesis of estrogens or interconversion

to estrogens, as well as the response of the testes to gonadotropins. Since natriuresis and sodium depletion can lead to elevations of circulating catecholamines which in turn could influence gonadotropin secretion, supplementation with small doses of potassium or carbohydrate is being examined in terms of preventing such events. The effects of protein supplemented fasting upon the hypothalamic-pituitary gonadal axis in men and women are also being examined.

## METHODS OF NUTRITIONAL STATUS ASSESSMENT

The establishment of improved methods for assessing the nutritional status of normal persons, as well as the patient population is an ongoing process. Investigators are currently examining the feasibility and accuracy of methods such as stable isotopes, nuclear magnetic resonance spectroscopy, etc., to better assess nutritional status. The use of nonradioactive stable isotopes appears to offer significant advantages over the radioactive methods previously used since they can be applied to normal volunteers.

Studies are under way to examine substrate metabolism and hormone action in vivo using stable isotopes and high magnetic resonance imaging (MRI). The specific aims of this research are to determine whether substrate cycling of glucose/glucose-6-phosphate and fructose-6-phosphate/fructose 1-6 diphosphate exists in man; to quantitate the contribution of these cycles to basal thermogenesis in man; and to determine whether thyroid and other hormones play a role in their regulation.

Using MRI, the intracellular milieu and therefore metabolism of the living organism can be directly observed. These findings from MRI studies will be compared with in vitro measurements of isolated liver and heart cell preparations in order to develop better MRI techniques to study the metabolism of organs in vivo. Such techniques will be useful tools in metabolic studies, and will have direct clinical applications in human investigations and diagnosis.

Stable isotope tracers in combination with gas chromatography and mass spectrometry are being studied for use in examining the physiology of amino acid transport and disposal, the conversion of essential to nonessential amino acids, and the fate of the nonessential amino acids in man; to evaluate the effects of nutrition, energy balance, and aging on these rates; and to investigate the pathology of these processes in diabetes and uremia. The data should allow for a more integrated picture of the quantitative dynamics of amino acid metabolism in man. Studies using these methods in infants receiving total parenteral nutrition will provide important data on the oxidation of essential amino acid in these infants and therefore their protein nutritional status. Stable isotopes using  $^{13}\text{C}$ -triolein are being evaluated as a diagnostic procedure for fat malabsorption in children, and are being compared to  $^{14}\text{C}$ -triglyceride breath tests currently used in adults.



The method of isotope dilution neutron activation analysis is currently being developed specifically for the accurate measurement of absolute levels of various stable isotopes of zinc, iron, and copper in human stools. The measurements obtained will be combined with a method based on nonabsorbable markers in order to provide an accurate fecal isotope balance method. Such a method would provide an accurate estimation of iron, copper, and zinc absorption under conditions of relatively low availability. The capabilities and limitations of the integrated method will be evaluated in adults.

A study of fundamental aspects of selenium nutrition and metabolism in healthy human adults is under way utilizing the new method of stable isotope enrichment and the concept of simultaneous double labeling. This novel tracer measures gastrointestinal absorption, urinary excretion, long-term body retention, the nature and quantitative significance of urinary metabolites, and the first pass effect of the liver. The dietary and host factors to be investigated are dietary forms of selenium and body selenium status.

The use of  $^{13}\text{C}$ -labeled tracers in nutritional status assessment is being studied in breath tests for use as clinical tools in the metabolic monitoring of nutritional disorders in the outpatient setting. In such tests, the  $^{13}\text{CO}_2/^{12}\text{CO}_2$  ratio is measured in breath following  $^{13}\text{C}$  labeled tracer ingestion; the rate and amount of  $^{13}\text{CO}_2$  release can be used as a quantitative measure to discriminate changes in metabolism between normal persons and patients. These data will be used to validate the use of a new ratio infrared spectrometer for the direct measurement of  $^{13}\text{CO}_2/^{12}\text{CO}_2$  and, therefore, as the instrument of choice in breath tests used to assess nutritional status.

Radioimmunoassay and receptor binding assays are being studied as appropriate methods for determining circulating levels of parathyroid hormone, calcitonin, vitamin D, and vitamin D metabolites in newborns and children. Computed tomography is being used to evaluate bone mass.

In order to enable physicians, who are prescribing nutritional support to critically ill patients, to obtain a daily assessment of their metabolic response to the prescription, a study is under way to demonstrate that net protein catabolism can be calculated accurately from BUN and serum creatinine. This method avoids the technical problems associated with daily urine collections. Protein balance of the patients is being measured in order to validate protein balance estimates based on a single pool mathematical model using urea nitrogen, BUN, and serum creatinine levels to calculate renal clearance, rates of urea production, and net protein catabolism. Since a good correlation between estimated and measured protein balances is anticipated, these data will improve the ability of the physician to accurately prescribe the best nutritional support regimen for specific patients. This study will also attempt to develop computer software that will relate the measured clinical and metabolic responses observed in patients, and visually display this information for the physician prescribing nutritional support. In addition, the study hopes to demonstrate that the daily review of the metabolic response

of patients to nutritional support will optimize the utilization of parenteral solutions and improve the quality of patient care.

#### NUTRITIONAL STATUS ASSESSMENT OF PATIENT POPULATIONS

Studies to assess the nutritional status of different patient populations hope to establish the specific nature of any nutritional problem that may underlie the disease, and the effectiveness of nutrition interventions or treatment that may be undertaken to improve health status. Maintaining an appropriate nutritional status is often very difficult in the cancer patient whose metabolic processes bear the brunt of tumor insult, chemotherapeutic measures and resultant anorexia.

One study of cancer patients is examining whether the elevated rates of protein synthesis are due to the additional protein synthesis by the tumor or to protein synthesis by the rest of the body. Whole body protein synthesis rates are being compared against the tissue fractional synthesis rates using  $^{15}\text{N}$ -glycine and  $^{13}\text{C}$ -leucine as tracers. In addition, the double labeled water method is being used to measure energy expenditure concomitantly with protein turnover in order to examine the relationship of protein turnover to energy expenditure.

In order to elucidate further the etiology of cancers of the larynx, esophagus, and oral cavity, a case control study is under way in order to identify the mechanisms by which alcohol increases the risk of these cancers; to determine whether host susceptibility to alcohol increases the risk of these cancers; to determine whether dietary deficiencies of vitamins A and C, zinc, iron, etc., enhance the risk of these neoplasms; to clarify the role of dental health in these neoplasms; etc. Detailed information on dietary intake, prior use of tobacco and alcohol, dental health, and other factors relevant to the etiology of these cancers are being considered.

Increased dietary intake of vitamins A and E, and beta-carotene have individually been associated with a decreased risk of carcinogen induced cancers. Vitamin E has been shown to have a regulatory effect on systemic vitamin A metabolism, and may also modulate beta-carotene conversion to vitamin A. A project is examining the extent and mechanisms of vitamin E regulation of vitamin A homeostasis by measuring the steady state pools of vitamin A and its metabolites in rat blood and tissues as a function of dietary vitamin A. High performance liquid chromatography assays, along with gas chromatograph/mass spectral assays, are being developed to monitor changes in vitamin A metabolites as a function of dietary vitamin E, with beta-carotene as the dietary vitamin A source, and with diets high in polyunsaturated fatty acids.

The retinoids and factors known to modulate them are also being examined in the azaserine-induced rat model of pancreatic cancer in order to better understand whether the retinoids exert a differentiating action on the pancreas. Markers of differentiation being



developed include levels of transglutamin, proteinase, and prostaglandins.

A 5-year randomized clinical trial is under way to evaluate the effectiveness of low dosage levels of isotretinoin in reducing the incidence of basal cell carcinoma in a high risk population, and to examine possible side effects associated with the long-term administration of these low doses. Approximately 1,800 subjects included in the study to be conducted at 10 participating clinical centers will be randomly allocated to intervention (10 mg/day of isotretinoin) or control. Recent case reports have shown that isotretinoin can prevent the appearance of new basal cell carcinoma for 4 years in patients at high risk of developing new tumors.

A number of studies under way to examine the reliability of different methods to obtain dietary intake data in epidemiological studies include various measures of nutritional status assessment to substantiate dietary intake information. In a study investigating dietary factors that may inhibit cancer of the colon and rectum, 350 colorectal cancer patients are being examined and dietary intake data are being collected by interviews designed to elicit recall of food intake 2-3 years prior to the interview. An effort will be made to validate this information through assays of fecal samples for levels of protease inhibitors, and hair will be assayed for various trace elements including selenium. Interactions among the dietary factors will also be correlated. Another study of colon cancer is comparing serum levels of vitamins A and E, and of selenium in individuals who developed colon cancer with levels of those who did not. Dietary intake information will also be collected on the frequency of eating foods in the past containing high amounts of vitamin A, beta-carotene, vitamin E, fiber and fat.

A study to evaluate the reliability of a food frequency questionnaire for use in retrospective studies of dietary intake and cancer prevention is under way. Dietary selenium, retinol, carotene, and alpha-tocopherol estimates obtained by the questionnaire will be compared to measured serum levels of these nutrients. The study has the potential to provide valuable methodological information on the validity of retrospective food frequency techniques that are being used in hypothesis generation for cancer prevention interventions.

Studies to establish the effects of nutritional status on the etiology of breast cancer include investigations on the relationship of dietary intake to hormone levels of teenage girls. Included in one study are 110 lacto-ovo-vegetarians and 125 nonvegetarians. The hormones being measured include total, albumin bound and free estradiol; total, albumin bound, and free testosterone; and steroids bound to sex-hormone-binding globulin. Ovulatory status will be determined, along with serum progesterone and urine pregnanediol. Possible confounding variables to be considered include age at menarche, time since menarche, medication use, height, weight, skinfold thickness, and physical fitness level. This study will provide insight on the role of diet in altering the hormonal milieu during the teenage years when the breast is particularly susceptible to carcinogens.

Components of tobacco smoke, primarily organic nitrates, nitrous oxide, cyanates, and cyanides are known to transform some forms of vitamin B<sub>12</sub> and folate coenzymes into inactive compounds. It has been suggested that exposure to cigarette smoke results in a localized vitamin B<sub>12</sub> and folate deficiency, limited primarily to the bronchial epithelium, thus making it more susceptible to neoplastic transformation by the carcinogenic hydrocarbons of tobacco smoke. A study is under way to investigate the presence of megaloblastic changes indicative of vitamin B<sub>12</sub> and folate deficiency in the bronchial epithelium of smokers; to investigate the effects of components of cigarette smoke upon B<sub>12</sub> and folate coenzymes in vitro; to demonstrate that the levels of B<sub>12</sub> and folates and their enzymes are lower in the bronchial epithelium of smokers as compared to normals; and to investigate the effects of B<sub>12</sub> and folate supplementation on the progression of dysplastic lesions of the bronchial epithelium of chronic smokers. It is hoped that lung cancer can be prevented by impeding or reversing the progression of preneoplastic lesions via an adequate supply of B<sub>12</sub> and folate to the exposed epithelia.

Studies on the relationship between biochemical measures of nutritional status and the occurrence of melanoma are testing the hypothesis that increased plasma levels of beta-carotene, alpha-tocopherol, and retinol, and increased red cell selenium reduce the risk of melanoma. Blood levels of carotene, retinol, alpha-tocopherol and lipids are being assessed in 200 patients with melanoma and compared with controls. Selenium status is being assessed using neutron activation of red cells. It is known that carotene modifies the effect of ultraviolet radiation, a possible risk factor for melanoma, and topical retinoids can cause regression of melanoma metastases.

Since persons with low levels of selenium are also thought to be at increased risk of cancers of the breast, lung, and large bowel, a study is under way of individuals in South Dakota to quantify the relationship of dietary intake of selenium with levels in the blood, urine, and toenails. Selenium blood levels and variability among individuals are unusually high in this population. Four duplicate samples of food ingested for 2 days once every 3 months will be collected in order to quantify the relationship of selenium intake and the concentration of selenium in blood, urine, and toenails.

The role of dietary selenium in cancer is also being investigated in a study under way in the People's Republic of China since it is known that dietary selenium intake is extraordinarily variable in China. This study will examine selenium status through the measurement of selenium intake and hair selenium, as well as the dietary intake of vitamins E, C, A, and beta-carotene, as well as vegetable fat since these nutrients are known to interact with selenium. Other nutrients to be studied because of their possible independent role in cancer include protein, total fat, dietary fiber, zinc, riboflavin and cholesterol. This study will permit an assessment of both an independent contribution of selenium to cancer, as well as a comparison of its effects with other nutrients.

Animal experiments looking at selenium status and cancer are considering the role of dietary fat in selenium activity, the role of selenium in azaserine-induced pancreatic cancer, the combined roles of selenium and fat in the more general aspects of the post initiation phase of carcinogenesis, the factors affecting selenium bioavailability, and the physiochemical properties of dietary fiber as related to selenium absorption.

Large scale clinical trials are under way to examine the effects of a 20 percent fat diet on disease-free survival and survival in women with stage II breast cancer who are currently entered on one of three adjuvant therapy protocols. All patients will undergo a complete nutritional status assessment that will include biochemical measures of nutritional parameters, anthropometric measures, and dietary assessment. A 2-month period of active intervention, i.e., two home and two group sessions to provide knowledge and necessary skills to develop and maintain the low fat eating pattern, will be provided to those persons randomized to the low fat group. Dietary compliance will be monitored by dietary intake scores and measures of lipoproteins. Followup examinations and testing for recurrences of breast cancer or additional primary cancers will be performed periodically.

Another study on the effects of the 20 percent low fat diet on the rates of recurrence and survival in women with breast cancer will assess the physiological effects of the diet in order to determine which subgroups of these cancer patients might improve their prognosis by adherence to a low fat diet. The effects of the diet on serum cholesterol levels and anthropometric measurements will be investigated as the variables that might play a key role in improving the prognosis for this special group of patients. The effectiveness of the techniques used to gain and monitor subject compliance with the low fat diet will be evaluated. Two types of nutritional counseling methods, i.e., individual and group, which use specific techniques to attain the low fat dietary intake of these trials, are being compared in terms of the recurrence rate in stage II breast cancer patients receiving adjuvant chemotherapy. The dietary habits of patients, prior to the institution of chemotherapy, are being recorded using nutritional histories and diaries. Patients will be evaluated monthly for fat intake during the treatment period, and every 3 months after chemotherapy is completed. Followup of patient compliance to the diet will continue for 5 years or until recurrence of the cancer.

In conjunction with the clinical trial of stage II breast cancer patients, one research group is establishing a statistical coordinating center while another is establishing a nutrition coordinating center. The statistical coordinating center will be developed in three phases. The first phase involves the development of the protocol for the recruitment, treatment, and dietary education of the patients, as well as the establishment of the data management and analysis plans. The feasibility phase will assess dietary compliance of 200 patients in the treatment group through the use of 24-hour dietary history measurements, using a personal computer for data



collection. The same data collection arrangement system would then be enlarged to accomodate a sample of 2,000 breast cancer patients. The Nutrition Coding Center at the University of Minnesota is developing the nutrition coordinating unit for the intervention trial. The first year will be devoted to protocol development and a feasibility study of 150 patients at three clinical centers.

Common protocols are being developed for the multicenter trial that will include three major areas involving nutrition: dietary intervention, dietary data collection for research purposes, and dietary data collection for counseling and adherence monitoring. A low fat food plan that can be individualized to meet food preferences of each patient, counseling strategies and supporting materials for achieving and maintaining the low fat diet, and training procedures for both the research and the intervention dietitians have been proposed. The dietary history technique is recommended as the method of choice for the research component of the trial, and frequent, randomly spaced, 24-hour recalls, collected by telephone interview, are proposed for compliance monitoring. The dietary data will be processed according to standardized procedures, and nutrients will be analyzed for compliance monitoring. Quality control procedures are being developed for each component of the dietary data control collections.

Investigations are under way to examine the correlates of ovarian cancer risks in approximately 300 women with ovarian cancer and 300 controls. The variables being considered include dietary habits using the semiquantitative food frequency questionnaires with particular emphasis on vegetable and animal fat, and vitamins; genital exposure to talc used as body or dusting powder; reproductive history including contraceptive use; use of phenobarbital and antidepressants; and family and personal histories. Biological measures include serum antibody levels to mumps, galactose transferase activity in whole blood, urinary gonadotropin levels in postmenopausal subjects, and selenium levels in toenail specimens.

A large prospective study of diet and cancer in women is attempting to quantitate the associations between dietary factors and site specific cancer rates. Particular attention is being paid to the relationships of amount and type of dietary fat with breast cancer, of vitamin A intake with cancer of all sites, and of the consumption of fat, fiber, and meat with colon cancer. The relationships between intake of other nutrients such as cholesterol and vitamins C and E as well as of specific food items such as coffee and artificial sweeteners, and the rates of a variety of cancers are being examined. Possible causal associations between other potential risk factors (including use of oral contraceptives, other hormones, prescription medications and hair dyes) and cancers of the breast, ovary, uterus, lung and melanoma will be quantified. This large prospective cohort study will allow precise and valid estimates of the effects of various dietary components and other risk factors on cancer causation or prevention.

Studies are being designed to ensure the accurate and efficient evaluation of the nutritional status of patients with advanced malignancy, and thereby allow for the most appropriate nutritional intervention. Perturbations of a variety of nutritional parameters in the patient with advancing cancer are being studied, along with the question as to whether these deficiencies are correctable by existing methods of nutritional intervention. A common core of nutritional assessment methods is being established for the cancer patient.

In order to better define the role of enteral nutrition in the treatment of protein-calorie malnutrition in cancer patients, a study is under way in patients with head and neck cancer to study abnormalities in protein and glucose metabolism secondary to continuous nasogastric feeding. Attempts will be made to determine whether increased resting energy expenditure, increased protein turnover, or abnormalities of carbohydrate metabolism impair the anabolic response of these cancer patients to continuous enteral alimentation.

Although food aversions are known to develop in cancer patients undergoing chemotherapy, the time interval surrounding treatment during which the aversion may develop, the types of foods most susceptible to this phenomenon, the persistence of these aversions, and the extent to which these aversions modify a patient's nutritional status have not been determined. In order to gain insight into these problems, four groups of 25 cancer patients are being studied. Two groups are being treated with therapeutic agents known to cause gastric distress and the other two are being given treatments not associated with nausea or vomiting. Information on the types and amounts of foods consumed in the 48-hour period surrounding chemotherapy will be obtained via a dietary recall and food record. At 1 week, 1 month, and 6 months post treatment, all subjects will re-rate the foods consumed during this period. The weight loss and treatment outcome of patients who develop aversions will be compared to those patients not forming aversions. The results of this research should help to increase our understanding of the nature of conditioned food aversions, and the potential for blocking their development. This information would thereby facilitate the development of dietary guidelines for chemotherapy patients, and to the extent that aversions influence nutritional status, improve the prognosis of such patients.

The mechanisms of cancer cachexia, i.e., the nutritional depletion and general deterioration of the cancerous host, are being examined in order to find ways of blocking or reversing the cachectic effects of cancer and thus make the cancer patient less vulnerable to anti-cancer therapies. Premature satiety is the immediate cause of the reduction in food intake in cancer patients and is possibly operating through an enhanced cephalic phase of satiety. Research has shown that body mass of these patients can be conserved and voluntary food intake increased by insulin treatment, without acceleration of tumor growth. Studies conducted in animals with sarcoma have shown that the cachexia is sarcoma dependent because if the tumor is removed, the cachexia can be reversed. A factor appears to be secreted from the sarcoma which mediates the anorexia and weight loss seen in



cachexia. In addition, exogenous insulin given to rats bearing sarcomas has been shown to increase spontaneous food intake, nitrogen balance, body weight gain, and does not promote tumor growth.

The assessment of nutritional status of persons at risk for coronary heart disease and cerebrovascular events is a major component of many current epidemiological studies. e.g., the Stanford Five City multiple risk factor reduction study, the Evans County Georgia study, and studies included in the SCOR program related to atherosclerosis. Longitudinal measures of dietary intake, alcohol consumption, tobacco use, weight for height, and physical activity are being compared over the long term in order to assess long-term risk factor changes in communities exposed to varying levels of educational intervention for coronary heart disease risk factor reduction. These studies are described in detail in the section of the report on Epidemiological Research in Nutrition.

Examinations are under way to track the etiology of high blood pressure from childhood to adulthood, and include repeat measurements of blood pressure, skinfold thickness, height and weight, along with extensive medical and psychological tests, dietary intake questionnaires, etc., beginning in children 2-5 years of age. A long-term randomized study of hypertension is designed to determine appropriate lifestyle modifications to lower blood pressure, as well as prevent its development in hypertension prone individuals ages 30-44 years. Intervention involves motivation and educational efforts to effect and sustain changes in lifestyle through improved habits of nutrition including reduction of salt intake, correction of overweight, and increased exercise to improve cardiopulmonary fitness. The primary end point of this study is to reduce mean diastolic blood pressure.

In order to gain a better understanding of the physiological nature of energy balance, body composition and the problem of obesity, studies are investigating the effects of hormones, and different dietary regimens as sources of energy. The obese Zucker rat is widely used as a model for obesity research, yet the energetics related to its adiposity have not been defined. Determinations are being made of total energy balance of adult obese and lean Zucker rats through measurements of energy intake, body compositional changes, total heat production, and total heat loss. Total heat production is separated into physical activity, thermogenesis, and the thermic effect of food ingestion using direct and indirect calorimetry techniques. The results of this research may be significant in identifying factors associated with genetically linked obesity.

Since the mineralocorticoids are potentially important in energy regulation, aldosterone is being studied in terms of its effects on fat deposition and lean body mass. The study will determine whether aldosterone infused over an extended duration results in progressive or limited effects, and if sex and age are interactive. Preliminary findings indicate that aldosterone alters fat metabolism by promoting deposition and inhibiting mobilization.

Normal young women consuming increasing amounts of energy under controlled conditions are being studied for differences in body composition by  $^{40}\text{K}$  counting, in resting metabolic rate, and thyroid hormone levels. These measures will be compared to changes observed in men studied under similar conditions. The questions to be addressed in this research pertain to the energy cost of weight gain, the metabolic response, and the relative proportions of lean and fat which constitute this gain. Body composition changes with obesity are also being examined, particularly in terms of the increase in lean tissue of the obese individual. Little is known as to its causes and whether the increase may be responsible for some of the metabolic abnormalities seen in obese individuals. Total body water,  $^{40}\text{K}$  assays, urinary excretion of creatinine and 3 methylhistidine, etc., are being measured in both obese and nonobese subjects.

Long-term serial data collected over 60 years concerning subcutaneous fat thickness obtained from fat biopsies, and estimates of total body fat obtained by underwater weighing are being analyzed in order to establish a normal pattern of fat distribution and loss for people from birth to 60 years of age. Measures of blood triglyceride and cholesterol levels will help to estimate the health significance of different levels and patterns of body fat.

In order to demonstrate the impact of dietary fat on steady state body composition, the carcasses of mice adapted to diets with a fixed protein but variable carbohydrate and fat content (12-83 percent of calories as fat) are being analyzed. Oxygen consumption and  $\text{CO}_2$  production measures are being taken in conjunction with measurements of nutrient intake. These data will help to establish how accurately carbohydrate, fat, and energy balances are maintained under ad libitum food intake conditions, as well as whether and how food intake may be altered in response to gains or losses in the animal's glycogen and/or fat reserves. These experiments test the hypothesis that an expansion or reduction of the adipose tissue mass represents an adaptation which influences free fatty acid levels until fat oxidation becomes commensurate on a percentage basis with a particular diet's fat content. If this hypothesis proves correct, long-term weight maintenance would be achieved due to the ubiquitous ability of the body for maintaining carbohydrate balance by mutual adjustment of food intake to carbohydrate oxidation and vice versa. Changes in the glycogen stores, however, barely affect body weight whereas alterations of the adipose tissue mass can lead to obesity. This research would help to develop metabolic evidence that a reduction in the diet's fat content may facilitate weight maintenance at a lower level of adiposity.

Studies in animals are determining how different protein diets may affect food intake through changes in the amino acid levels of the blood and brain. The effects of meals containing amino acids that compete for uptake into the brain are being studied for their ability to influence the amount of protein consumed by rats that are subsequently offered their choice of two diets differing in protein content. Also, diets differing greatly in protein content will be studied for changes in blood and brain amino acids and serotonin and

catecholamine content. Amino acids that influence food intake or preferences will also be infused directly into the brain in order to determine whether they affect feeding behavior. The effects of alterations in the brain amino acid pool (by either dietary imbalances of amino acids or changes in total protein intake) on the integrity of protein synthesizing systems and therefore on protein synthesis and turnover will be examined in vitro and in vivo.

Protein diets have often been used for the treatment of obesity; however, the effects of prolonged use of these regimens on the preservation of total body nitrogen has not been established because of restrictions imposed by currently available methods for nitrogen balance studies. Consequently, the effects of a hypocaloric carbohydrate diet on nitrogen equilibrium remains controversial. Sixty obese subjects consuming either a protein or a carbohydrate diet for 3 months are being studied in order to determine the effects of the protein diet on nitrogen balance as compared to an equicaloric carbohydrate diet. This period will be followed by a refeeding and weight maintenance phase for an additional 3 months. Integrated changes in nitrogen balance will be determined by a new noninvasive technique.

Another investigator is examining the phenomenon that when diets are low in protein, i.e., at or near the requirement for maintenance, a thermogenic response is elicited which results in the inefficient utilization of other energy yielding dietary constituents. For example, in some rodents under these conditions the activity of brown adipose tissue is increased and involved in dietary induced thermogenesis, however, its precise role is unclear.

Other studies examine whether a weight reduction diet low in fat or carbohydrate decreases energy expenditure in obese adults. These investigators are also examining the role of altered thyroid hormone levels and sympathetic nervous system activity in mediating the decrease in energy expenditure, as well as comparing energy expenditure in obese subjects before and after weight loss with those of lean subjects. The effects of different diets on energy metabolism will be determined by expressing energy expenditure per unit of whole body potassium or whole body nitrogen content.

Studies of energy expenditure under way in uremic patients involve the assessment of clinical and nutritional status, energy expenditure, energy requirements, and the metabolic response to high energy intakes, starvation and glucose free dialysate. Urea kinetics during hemodialysis are being investigated. Methods for estimating net protein catabolic rate from pre- and postdialysis serum urea, body weight, and dialyzer kinetics are being evaluated.

Studies of food deprivation in preweanling and adult rats show marked but opposite changes in liver responsivity to the alpha- and beta-adrenergic agonists. Research is under way to investigate the possibility that nutritional status is an important regulator of end organ responsivity to sympathetic antagonists in developing and adult animals, and to examine the role of specific nutrients in the altered responsivity that occurs with food deprivation.



Osteoarthritis is characterized by a chronic degradation of articular cartilage in the afflicted joints, with arylsulfatases A and B elevated in the articular cartilage. Vitamin C has been found in tissue cultures to inhibit the activity of the arylsulfatases. This inhibition will be explored in the knee cartilage of animals kept on various levels of dietary vitamin C in order to determine at what level ascorbic acid may be helpful in the treatment of osteoarthritis.

Bone changes in young adult women are being investigated since bone loss is thought to occur at an annual rate of 0.6 percent. The low calcium intake of the population, as well as other nutritional factors are thought to play a role in this ongoing bone loss. Nutritional histories and 24-hour recalls, as well as physical activity are being measured with concomitant measurements of 24-hour urinary calcium and hydroxyproline, parathyroid hormone, estrogens and vitamin D metabolites. The data will indicate the relation of premenopausal bone changes to calcium and vitamin D status, and ultimately the potential impact of nutrition, activity and oral contraceptive use on this loss.

Studies are under way to improve our understanding of the factors that regulate the renal biosynthesis of  $1,25(\text{OH})_2\text{D}_3$ , a key hormone in calcium homeostasis and bone mineralization. In <sup>3</sup>vitro studies of various hormones, primarily parathyroid hormone, and calcium and phosphate ions which regulate  $1,25(\text{OH})_2\text{D}_3$  production will be carried out. Since diets low in calcium or phosphorous are known to stimulate the enzyme 25-hydroxy-1 hydroxylase, the effects of such diets on cell calcium fluxes and changes in cytosolic calcium will be studied.

The levels of fatty acids of the omega-3 or alpha-linolenic acid family appear to be high in the retina and cerebral cortex, thereby suggesting an important role for them in the function of neuronal and photoreceptor membranes. Studies in rhesus monkeys are testing the effects of a dietary deficiency of omega-3 fatty acids using biochemical, electrophysiological and behavioral techniques. The levels of the fatty acids in plasma lipids, erythrocytes, etc. are being monitored, while retinal function is being evaluated with rod and cone electroretinograms, and behavioral tests of vision and learning are being carried out. This research will provide important data on the nature of a dietary requirement for the omega-3 fatty acids in primates.

Patients with cirrhosis, unlike healthy adults, require cysteine and/or tyrosine as essential amino acids but in many cases the enteral and parenteral solutions provided to these patients are often lacking in the two amino acids. Studies are under way to determine simple pharmacokinetic tests to identify those cirrhotics who are deficient in these two amino acids in order that appropriate feeding preparations can be developed. Such tests will help to improve the nutritional status of these patients, and alleviate some of the morbidity and mortality related to this condition.

Due to the nature of research on nutritional status assessment, many studies described in this area are also described under the categories of epidemiological research in nutrition, and nutrition and prevention of disease.

In epidemiological surveys and studies of populations, nutritional status assessment measures include methods to screen individuals as well as to assess and monitor populations. When either an intervention program or survey is undertaken, standardized data collection and adequate data handling facilities ensure quality information that is available rapidly for analysis and utilization. Well documented data made available to agencies and scientists involved in studies of nutritional epidemiology facilitate improvements in such studies. Intervention projects to assess dietary intake and nutritional status also requires data on food composition that accurately reflects the nutrients found in the food supply. Determining the reliability of food composition data along with food consumption data is an ongoing process.





## APPENDIX F

### EPIDEMIOLOGICAL RESEARCH IN NUTRITION



## EPIDEMIOLOGICAL RESEARCH IN NUTRITION

Epidemiological research in nutrition examines the role of food habits and the socioeconomic factors that influence food selection in health and disease conditions of various populations. These studies utilize dietary intake data and biochemical and anthropometric methods to assess nutritional status in an attempt to determine the relationship of diet to nutritional status and the subsequent development of specific diseases or conditions. Traditionally, much of the research supported in this area has included the following five categories: 1) studies to evaluate methods and procedures; 2) studies of nutrition's role in the physical and psychological development of defined populations; 3) studies on the relationship of maturation and reproductive functions to nutrition; 4) surveys of nutrient intake and nutritional status assessment of special population groups; and 5) studies on the relationships of food intake to the development of disease.

In FY 1984, a number of clinical intervention trials were initiated in order to examine the long-term effects of specific diets on disease etiology, especially in high-risk populations, or to examine the effects of a specific nutrient or non-nutrient food component on disease. For example, clinical trials are under way to investigate the role of a low fat diet in preventing breast cancer in postmenopausal women, a high fiber diet in preventing colon cancer, and the effects of different sodium regimens in preventing hypertension.

In FY 1984, NCI, NHLBI, NIA, NIADDK, NIAID, NICHD, and NIDR supported projects with significant epidemiological nutrition research components in the amount of \$35 million or 18 percent of total nutrition research.

### METHODS AND PROCEDURES

Studies are under way to evaluate methods and procedures used in epidemiological research related to nutrition. The methods being examined include those designed to increase the validity and reliability of dietary intake data, food composition analysis, and body composition measures. In order to develop better methods of dietary data collection in free living individuals, one investigator is examining a microcomputer for its effect on improved accuracy and increased efficiency in the collection of dietary data. The microcomputer system will incorporate various features developed by the Nutrition Coding Center at the University of Minnesota, and used for the collection of dietary data including verification, error checking, and quality control. The system incorporates the USDA nutrient data base as a standard reference to permit interfacing with either the Nutrition Coding Center or the USDA food composition tables. It is thought that the microcomputer-based system will result in improved documentation of food intake, more accurate coding, and more cost effective collection and processing of dietary data. These hypotheses will be tested and evaluated at both the coding and the interviewing levels. A feasibility study will explore the potential use of the system in the home or clinical setting.



A standardized system for the collection and processing of dietary information is being developed which includes coding dietary data and calculating nutrients according to the data base maintained at the Nutrition Data Center. The system includes a recipe file, a manufacturer's file of nutrients and ingredients of commercial products, and an "uncodables file" for standardization of infrequent coding decisions. The Nutrient Data Base includes approximately 1,500 items and 60 nutrients obtained from USDA, as well as from other standard references and food manufacturers. The system allows for the characterization of the type and quantity of dietary fat and cholesterol, by specification of the type and brand of fat used in recipes, fats added in food preparation, and estimates of amount of fat absorbed in various food preparation methods.

Additional methods being investigated for their accuracy in obtaining dietary intake data include the semiquantitative food frequency questionnaire, a self-administered dietary data collection instrument, and a retrospective food frequency instrument.

One project is under way to develop and validate a self-administered dietary data collection instrument for use in chemoprevention trials which is specific to the nutrients of interest (vitamins A and C) and specific to the dietary patterns of 80 young adult women in Tucson, Arizona. Dietary data obtained from the questionnaire will be compared against the NCI core dietary questionnaire and a dietary record kept for 8 days, with particular attention paid to intakes of vitamins A and C, portion sizes, and specific foods consumed. The results of this analysis will be used to develop a protocol for revising the questionnaire to cover other nutrients and/or study populations, and to maintain quality control on questionnaire data in a longitudinal study. This study will also examine the relationships between plasma nutrient levels and usual dietary intake as obtained by the questionnaires and the 8-day dietary record.

The validity of retrospective food frequency techniques used in hypothesis generation for cancer prevention interventions is being examined. Intake measurements of dietary selenium, retinol, carotenes, and alpha-tocopherol obtained from the food frequency questionnaire is being compared with measures of serum levels of these nutrients in 199 cancer cases and 398 matched controls. The mailed food frequency questionnaire elicits information on usual serving sizes and frequency of consumption of selected foods and food groups. The validity of the nutrient intake measures will be assessed by analyzing the association between serum nutrient levels and computed estimates of nutrient intake based on the food frequency questionnaire.

Other studies concerned with the reliability of dietary intake data are looking at inter- and intraindividual variability in dietary recall by using the same questionnaire after a 10-year period. The results of this research will provide some insight as to whether dietary data collected today is a reliable indication of foods consumed in the past.

Research on food composition analysis includes efforts to validate a new analytical method for low-cost nondestructive multielement analysis of solid and liquid foods using x-ray fluorescence analysis. This study will be expanded into a phase II study needed to provide more data on the analysis of trace elements, as well as to assess the possible use of this method for widespread commercial application in industrial food testing, processing, quality control, and regulatory and labeling needs.

Another project, to establish a data base on vitamins and minerals that can be easily updated and serve as a comprehensive reference for monitoring the intake of vitamin and/or mineral supplements of individuals, capitalizes on the unique nature of the universal product code (UPC) marking that appears on practically all common vitamin/mineral preparations, as well as on other more exotic dietary supplements such as bone meal and kelp. The nutritional supplement information in the data base will be identified by the UPC code. The nutrient information on various products will be converted to a common basis for the analysis of dietary intake information, regardless of the manufacturer's labeling information. The utility of the data base will be tested through a survey of nutritional supplements users. The eventual availability of the data base through commercial channels is under consideration.

A new statistical method, "Structured Exploratory Data Analysis" capable of analyzing patterns of familial similarity and gene-environment interactions is being used to analyze data sets from nine U.S. populations in order to determine the relative strengths and forms of various influences that affect the familial aggregation of cardiovascular risk factors. The data analyzed include blood pressure; plasma lipid, lipoprotein, and cholesterol concentrations; weight; and a variety of cultural and environmental variables including diet, stress, physical activity, smoking behavior, and measures of knowledge, attitude, and opinions that relate to nuclear family sets. This analysis allows for the selective consideration of trait characteristics for cardiovascular disease across families, and thereby will help to provide strategies to most effectively approach their modification.

#### PHYSICAL AND PSYCHOLOGICAL DEVELOPMENT OF INFANTS AND CHILDREN

Nutrition's role in physical and psychological development is being investigated in a number of studies related to infant and maternal nutrition. Epidemiological studies of infant feeding practices and food consumption patterns of normal infants are under way to determine their effects on growth and development, as well as to identify dietary determinants in infancy that may play a role in the etiology of diseases later in life. Under examination are studies on: the effects of chloride deficient infant formulas on infant development; the impact of malnutrition on the infant's risk of developing meningitis; and the epidemiology of infant botulism, anemia in African children suffering from schistosomiasis, childhood obesity, and dental caries.

Infant feeding practices are being assessed in terms of the incidence of breast and bottle feeding among different Bedouin tribes who are changing from a seminomadic to a sedentary lifestyle. Data collected from 2,500 women shortly after giving birth and from a subsample of women at 5-8 months after birth include background information on perinatal events and delivery complications, prior history of infant feeding practices, and infant feeding practices regarding the current child. Followup data have been collected on changes in infant feeding practices over time and on intercurrent morbidity, especially gastroenteritis and respiratory disease resulting in hospitalization. The data collection is complete and the collected information has been computerized and is undergoing preliminary analysis.

Information on infant feeding practices and growth is being collected on 600 women of North African descent and their newborns. The information includes interviews at 6 months and 9 months of gestation, reports on the status of the newborn, any complication in delivery, as well as anthropometric measures collected during pregnancy and on newborns.

In order to identify various factors influencing food consumption of normal infants and to obtain additional information on their nutrient requirements, a study is providing formula fed infants with formulas that differ only in one of the following parameters: energy concentration, type of carbohydrate, quantity of an amino acid, or quantity of a trace mineral. The quantity of the milk consumed each day will be measured, and anthropometric and biochemical measurements will be performed at regular intervals. Metabolic balance studies of these infants will determine the interaction between trace minerals in influencing their absorption and retention.

An epidemiological study on the relationship between type of infant milk feeding (human milk, cow's milk, or commercial formula) and serum cholesterol levels of U.S. children age 4-11 years is under way to determine if the high cholesterol content of breast milk sets up homeostatic mechanisms that allow for effective cholesterol metabolism in adult life. Findings from this study will be important for identifying early dietary determinants of childhood serum cholesterol levels.

Infants who have suffered from hypochloremic metabolic alkalosis while exposed to the two chloride deficient formulas, Neo-Mull-Soy or Cho-Free diets, are being identified on the basis of hospital discharge diagnoses for the period of July 1, 1978, through December 31, 1979, using CPHA/PAS, CHAMP, etc. and are being compared to infants exposed to the chloride deficient formulas without developing the metabolic alkalosis. The variables assessed include physical growth and development, cognitive development, dentition, gross and fine motor development, neurological competence, learning, school achievement, speech development, and use of language.

Since malnutrition predisposes the infant to infection, a poor nutritional status and the lack of breastfeeding have been suggested as



risk factors for meningitis, one of the most serious infectious diseases seen in children in the U.S. Treatment of the disease routinely involves starving infants for 7-10 days despite the stress of infection and the needs of ongoing brain growth. A study is under way to examine risk factors related to nutrition in the acquisition of Haemophilus influenzae type B meningitis and the nutritional penalty incurred in the course of treatment. The nutritional status of the infants on hospital admission will be assessed by measuring height, weight, mid-arm circumference, tricep skinfolds, and hair zinc. To supplement this information, birth weight, growth histories, breast-feeding history, the use of drugs and/or vitamin or mineral supplements, and qualitative dietary intake of the infants will be recorded. Followup assessments of the nutritional status of these infants will be made at 1, 3, and 6 months.

Data suggest that infant botulism may be the prototype of a class of diseases caused by various toxin producing Clostridia that colonize the infant gut and whose toxins are capable of causing the symptoms of sudden infant death syndrome. Research is under way to elucidate the epidemiology of infant botulism, to identify associated host and environmental risk factors, and to apply this knowledge to the design of preventive measures applicable to infant botulism and other toxigenic intestinal infections of infancy. The hypothesis that human milk offers protection against sudden death from infant botulism is being studied.

Since the adverse effects of schistosomiasis on nutritional status has not been well documented, the role that Schistosoma hematobium infection and its treatment plays on anemia and growth retardation of children is being studied in 1,000 primary school children in Kenya. Physical fitness and urinary iron loss will be related to the magnitude of the infection, and the hematological and growth response to treatment will be assessed.

Data on growth velocity of Samoan children living in California who were 0-5 years old in 1971, and those born since 1971, are being collected in order to estimate secular trends in growth. The nutritional data collected on the children include complete anthropometry, blood pressure, heart and lung auscultation, thyroid palpation, food intake data, etc. Preliminary data suggest that diastolic pressures were higher than should be expected from a sample of children this age.

A longitudinal cross sectional study of childhood obesity is examining the relative contributions of genetics and nutritional factors to its pathogenesis. Data are being collected on metabolic and body composition differences between obese and nonobese children since recent studies have shown that body composition changes with the recovery from anorexia nervosa. Determinants of continuities and changes in fatness over specified age periods, sex, and in the context of the family are being examined. These determinants include dietary habits, socioeconomic variables, marital affinities, domiciliary arrangements, lifestyle, and family composition.

A study to examine childhood obesity in terms of prior eating and physical activity patterns, and parental attitudes to prior body measurements has collected data related to dietary habits, physical activity, anthropometry, and parental attitudes about eating activity etc., on children from the age of 6 months to 9 years. Critical periods for obesity development will be identified and longitudinal patterns of diet, physical activity, body measurements, growth and sociocultural factors will be analyzed in relation to fatness/leanness. Other epidemiological studies are designed to develop appropriate procedures to control body weight in high risk children and to prevent adult obesity.

A longitudinal study to investigate food intake patterns and the incidence of dental caries is under way in 800 11-to 12-year-old children who live in a community where the drinking water contains 0.3 ppm. fluoride.

## MATERNAL NUTRITION

Epidemiological studies related to maternal nutrition include investigations on reproductive function; the effects of maternal PKU on pregnancy outcome; the pathophysiology and physiology involved in the diabetic pregnancy; the influence of maternal zinc deficiency on infant growth and development, immunohematological function, and behavioral development with specific attention to potential developmental disabilities; the link between vitamin supplements taken in the periconceptual period and the risk of neural tube defects; the effects of prenatal fluoride supplements in preventing the development of dental caries in the primary dentition; and the patterns of maternal diet, alcohol and tobacco use during lactation in relation to infant growth and development.

Studies are under way to determine the level of maternal phenylalanine which maintains a normal pregnancy; at what stage of pregnancy a low phenylalanine diet is most effective in preventing the effects of maternal PKU on the developing fetus, i.e., if the beneficial effects of a low phenylalanine diet can be improved when initiated prior to conception compared to postconception; and whether the diet reduces the frequency of mental retardation, spontaneous abortions, low birth weight, congenital malformation, neurological and behavioral impairments found in infants of mothers with hyperphenylalaninemia. The study is also examining serum levels of tyrosine and trace metals during pregnancy and the effects of supplementation, provided when levels are low, on pregnancy outcome.

## NUTRITION OF SPECIAL POPULATION GROUPS

Surveys of nutrient intake and the assessment of nutritional status of special population groups are under way in studies of esophageal cancer in China, gallbladder cancer in Hispanics, and diabetes and obesity in Pima Indians. Data collected from the Initial Followup of the National Health and Nutrition Examination Survey and the



continued followup of NHANES I, and NHANES II are currently being analyzed in order to test various hypotheses on the relationship of dietary practices to the incidence of diseases such as cancer, cardiovascular disease, obesity, and osteoporosis as well as diet's effect on overall health and longevity. This research is described in detail in appendix G.

#### THE RELATIONSHIP OF NUTRITION AND DISEASE STATES

Epidemiological methods are being utilized to examine the possible role of nutrition and the relationship of food intake to diseases such as cancer, cardiovascular disease, diabetes, osteoporosis, obesity and oral diseases. A number of crosscultural surveys and case control studies are under way to examine the relationship of nutrition to cancer etiology. Populations from the U.S., Finland, Yugoslavia, Finland, Colombia and Japan are being studied. The dietary habits being examined in these populations include consumption of specific food groups and food items such as meat, fruits and vegetables, ethnic foods, and coffee; as well as specific nutrients such as fat, vitamin A, cholesterol, folacin, and trace minerals. These studies also investigate general nutritional status through anthropometry and biochemical indices, and examine food storage and cooking practices.

Studies to examine the role of diet in cancer etiology are under way in geographical areas with unusually high site-specific cancer mortality, conceivably related to diet, and among migrants such as Oriental-Americans whose changing cancer rates appear to be related to new lifestyles. Examples of studies of diet and cancer in high risk geographical areas are investigations of gastric cancer in blacks of south Louisiana, lung cancer in steelworkers of Pennsylvania, oral cancer in women of North Carolina, respiratory cancer in residents of New Jersey and coastal Texas, and esophageal cancer in persons in South Carolina, etc.

The study of cancer rates of 8,000 Japanese men living in Hawaii is looking at the relationship of dietary practices, serum levels of various nutrients, and cancers of the stomach, colon, lung, prostate, rectum, etc. Other studies of diet and cancer are examining the multiethnic populations of Hawaii.

Long-term studies on the role of diet and lifestyle characteristics in the etiology of cancer are focusing on the Seventh-Day Adventists, who refrain from coffee, refined foods, hot spices, smoking and alcohol, and who follow a lacto-ovo-vegetarian diet high in vitamins A and C, and low in saturated fat. One study is examining the reliability of dietary recall methods by comparing data collected over 7, 10, and 23 years of Seventh-Day Adventists who have cancer and those who do not.

A number of case control studies have been initiated to examine the role of diet and nutrition in cancer etiology, particularly in relation to colorectal cancer and breast cancer. One 3-year case control

study is evaluating the respective roles of, and possible interactions between, dietary habits and physical activity in the etiology of adenocarcinoma of the colon. Specifically, the study is designed to test the hypotheses that: (a) physical inactivity increases the risk of colon cancer, especially of the left side of the colon, and (b) physical inactivity acts as a modifier or as a confounding factor in the relation between dietary factors and colon cancer risk. Dietary habits to be examined include past frequency of consumption of fats--total, saturated and polyunsaturated; beef and all meats; milk and other dairy products; dietary fiber; cruciferous vegetables; and vitamins A, C, and E. Information about drug use, medical history, and lifetime physical activity levels, both at leisure and at work, will be collected for the 30 years prior to the diagnosis.

Another case control study of site-specific colon cancer will compare 400 cases of colon cancer to 400 controls with cancer of sites other than gastrointestinal or breast, and 400 general population controls in order to test the following hypotheses: 1) dietary patterns including high fat, high meat, low vegetable (particularly cruciferous) consumption are positively associated with risk of colon cancer; and, that; 2) cholecystectomy is positively associated with right-side colon cancer. Other potential risk factors to be explored include urban living and residential migration, history of intestinal disorders, medicinal drug use, body weight, socioeconomic status, and ethnicity.

This same data set will also be utilized in a case control study of breast cancer, since both colon and breast cancer are related to the same risk factors. The availability of data on lifetime residential histories offers the special opportunity to investigate the cumulative and temporal nature of urban living as a risk factor for colon and breast cancer.

Other studies on the mechanisms by which dietary factors affect colon cancer are investigating specific quantitative and qualitative parameters in fecal bile acid patterns and fecal mutagens and their relation to dietary fat and fiber intake.

Studies on the effects of a low fat diet (20 percent of the calories as fat) on the development of breast cancer are under way in the high risk group of postmenopausal women, who will periodically complete the semiquantitative food frequency questionnaire (SFFQ), as well as a 3-day dietary record in order to determine dietary compliance. Serum lipids, i.e., total cholesterol, HDL and LDL cholesterol, and triglycerides will be examined since the low fat diet should produce lower serum cholesterol levels as well as shifts in HDL and LDL cholesterol. Annual blood determinations of estrogens (estrone, estradiol, and free estradiol), and apolipoproteins (A-1 and B) will be made. One objective of this effort is to obtain an accurate analyses of nutrient intake in order to provide advice, training, and written materials to the nutritionists in order to assist them in improving compliance with the low fat dietary regimen. The biochemical measurements will provide an additional measure of dietary adherence, and will permit comparison of serum lipids and estrogen levels with dietary parameters and the clinical occurrence of breast cancer.

In order to test the efficacy of the low fat dietary regimen on reducing breast cancer, a project is under way to develop and evaluate a statistical coordinating unit (SCU). The SCU will be examined in terms of its usefulness in developing eligibility and exclusion criteria for study participants, enhancing recruitment and compliance of participants, providing randomization procedures and services, monitoring success at reaching dietary goals in the low fat diet group, developing unbiased procedures for endpoint determinations and monitoring, and reporting the efficacy of the intervention if the long-term phase of the trial is undertaken.

Other studies of breast cancer etiology are investigating whether specific hormonal profiles in plasma and breast fluids are linked to diet. Studies which modify types and amounts of dietary fat and examine their relationship to corresponding hormone changes are designed to gain a better understanding of the mechanisms whereby fat may enhance tumor development in the breast. Another case control study is addressing the hypothesis that vitamins A, C, and E, zinc, selenium, fiber, and protease inhibitors are negatively associated with breast cancer and that certain interactive effects among the nutrients may play a role in the etiology of this disease.

Based on animal and in vitro experiments that have demonstrated that selenium supplements reduce the incidence of carcinogen induced and spontaneous neoplasms, a prospective study of selenium status of 122,000 married registered nurses has been initiated.

The hypothesis that increased red cell selenium and plasma levels of beta-carotene, alpha-tocopherol, and retinol reduce the risk of malignant melanoma is being investigated in a case control study which also includes the collection of dietary intake data. The relationship of dietary data and the biochemical measures with the occurrence of malignant melanoma is being examined.

A case control study of nutrition as a risk factor for prostate cancer in white urban males, age 45-75 years, is using histologically confirmed cases of adenocarcinoma of the prostate identified through the Utah cancer registry. Information will be collected from cases and controls on food frequency, both before illness and during adolescence, along with data on family history, prior viral infections, sexual factors, occupational exposure to metals, etc.

To examine the etiology of gallbladder cancer in Los Angeles County Hispanics, data are being collected on reproductive history, estrogen levels, Hispanic diet, American Indian inheritance, past gastrointestinal and metabolic disease, and environmental exposures. The study will consist of all cases of gallbladder cancer occurring in females in Los Angeles in a 3-year period; controls will consist of matched persons chosen from the neighborhood of the case as well as matched cases undergoing cholecystectomy at the hospital in which the cancer case was diagnosed.



A case control study of alcohol as a risk factor for laryngeal-hypopharyngeal cancer will evaluate the relative carcinogenicity of various alcoholic beverages, comparing clear liquors (vodka, gin, light rum) which have few contaminants or congeners with smoky liquors, beer, and red and white wine. This study, which will include 750 cases of laryngeal or hypopharyngeal cancer and three controls per case from the Boston area, hopes to determine to what extent the increased risk of cancer with alcohol intake is attributable to the ethanol content versus possible contaminants or congeners.

Two intervention trials to examine the use of vitamin/mineral supplements to reduce esophageal cancer incidence and mortality are being carried out in the region of Linxian (Hena province) of the Peoples Republic of China. This area has the highest rate of esophageal cancer in the world, and it seems likely that the population's chronic deficiencies of several nutrients may be etiologically involved in the disease. The effects of the supplements on regression/progression of esophageal dysplasia, total cancer incidence, cancer mortality, and total mortality will be examined in one trial of 2400 patients diagnosed with esophageal dysplasia, as well as in a second trial of 28,000 persons in the general population.

The U.S. Finland cancer studies are attempting to determine if supplementation with beta-carotene, vitamin E, or both, is effective in preventing lung cancer in smokers; to assess the role of dietary selenium, vitamins A, E and C, and fat in breast cancer development; and to evaluate the overall relationship between various levels of nutrient intake and subsequent cancer risk.

A randomized clinical trial to examine beta-carotene as a preventive agent in lung cancer is being conducted in a high-risk cohort of men occupationally exposed to asbestos, and a selected group of hospital patients with abnormal sputum cytopathology. Bronchial epithelial changes, evaluated by repeated sputum cytology, are being used as the measure of response to the chemopreventive agent. Serum levels of beta-carotene are being studied with respect to the degree of sputum metaplasia or dysplasia found at initial examination, and with respect to bronchial epithelial changes throughout the clinical trial.

An ongoing study of diet and cancer is being conducted among a cohort of U.S. female registered nurses, currently between the ages of 38-63 years. The dietary aspect of the study began in 1980 with the completion of the semiquantitative food frequency questionnaire by 96,000 participants. The questionnaire was found to be reproducible, and correlated reasonably well with a series of one week diet records and selected biochemical parameters. In order to better test a variety of hypothesis relating dietary factors (total, saturated and polyunsaturated fat, protein, dietary and crude fiber, carotene, preformed vitamin A, vitamins C and E, cholesterol, coffee, and alcohol) to the incidence of cancers of the breast, colon, lung, and malignant melanoma, one component of the study will reassess dietary intake among the cohort using an expanded more detailed and optically scannable SFFQ. The second component of this study is a detailed documentation of dietary and biochemical parameters of 150 partici-

pants, who have completed 1 week dietary records using the expanded SFFQ and twice provided blood for a variety of biochemical measures of nutritional status during the first year of the study and again after 2 years. These data will provide estimates of short and long-term variability of dietary intake and therefore will quantify any misclassification associated with SFFQ. After 4 years of followup, relative risks of nutrient distributions will be detectable for cancers of the breast, colon, and lung respectively.

Two studies of seventh graders are evaluating various cancer prevention programs aimed at reducing the long-term risk of cancer by preventing the onset of smoking, and by reducing heavy alcohol consumption in conjunction with smoking. The first study will evaluate the effects of three prevention programs (i.e., smoking prevention, drug abuse prevention, and healthy lifestyle promotion) provided by the schools with and without family involvement, on cigarette smoking, alcohol and marijuana use, and other health related behaviors in students and their parents. The second study will test the effectiveness of a cancer prevention television series delivered via commercial television to the entire Los Angeles basin, with and without additional school prevention programs, on the dietary habits, smoking behavior, and related health behaviors of a second cohort of seventh graders.

Epidemiological studies are under way to gain more insight on the etiology, prevention, and treatment of coronary artery disease, atherosclerosis, and hypertension. Lipid Research Clinics are being established and maintained to provide an increased understanding of the diagnosis and management of hyperlipoproteinemia and to establish opportunities for further research into the causes and treatment for coronary artery disease.

Offspring of the Framingham Heart Study are being studied in order to assess their cardiovascular function, cardiac structure, personal habits including diet, and general physical condition. This research will provide information on the incidence, precursors, and etiology of subclinical endpoints that are used as indicators for drug therapy and other kinds of intervention to prevent cardiovascular disease.

In order to determine the etiology and pathogenesis of atherosclerosis and its sequelae, a number of morphological, epidemiological, immunochemical, and biometric methods are being combined. The possible etiological relationships of certain environmental factors and arterial lesions, coronary heart disease and sudden death are being studied using a community pathology report.

A multidisciplinary approach to elucidate factors related to the etiology of atherosclerosis is under way in the SCOR program; one component of which includes epidemiological and genetic studies of well characterized pediatric populations. One study on the early natural history of risk factors for atherosclerosis and essential hypertension will examine the incidence, prevalence and tracking of hyperlipidemia, hypertension, and obesity in a school age well-defined biracial population of 5,000 with emphasis on the familial aspects of lipoprotein hemodynamic abnormalities.



Surveillance data on the morbidity and mortality related to all clinical cardiovascular and cerebrovascular events; i.e., transitory ischemia, CVA, myocardial infarction along with the collection of pathological specimens and other necropsy data are being collected from all cohort study groups of Evans County, Georgia. Food intake data and blood serum levels will be analyzed by a number of institutions interested in exploring the association between the observed coronary heart disease and hypertension in the Evans County study population.

The Stanford Five City multiple risk factor reduction study is a 6-year education intervention program aimed at lowering cardiovascular disease risk and an 8-year survey and surveillance evaluation of risk factor levels of persons living in Salinas, Monterey, San Luis Obispo, Santa Maria, and Modesto. Secular trends in rates of fatal and nonfatal cardiovascular disease will be examined. Another surveillance study of environmental, behavioral, cultural and socioeconomic variables related to cardiovascular disease is under way in Minneapolis and St. Paul, Minnesota.

A case control study to examine the interrelationships of alcohol consumption, lipoproteins, personality type, diet, vasectomy in the etiology of myocardial infarction is under way. The relative risk for myocardial infarction of moderate alcohol consumers as opposed to nondrinkers is being examined when HDL and other established risk factors are controlled. The role of dietary factors as determinants both of myocardial infarction and of other risk factors will be analyzed.

Another study of 40,000 men and women is under way to elucidate the role of glucose intolerance as an independent risk factor for cardiovascular disease, and to clarify the role of hyperuricemia, obesity, rapid resting heart rate, pure systolic hypertension, and ECG abnormalities as risk factors. The relationship of glucose intolerance as well as clinically diagnosed diabetes, and each of the other traits to mortality from cardiovascular disease, coronary heart disease, sudden coronary death and cerebrovascular disease and cancers are being examined. This endeavor is also part of an International Collaborative Group involving 15 prospective epidemiological studies under way in Australia, Europe, Japan and the U.S.

Genetic and environmental factors related to hypertension are being examined in a study of spouses and children of identical twins. The aims of this research is to partition the genetic and environmental contributions to the tendency for blood pressure to increase with age, and to examine the relationship between estimates of sodium and potassium intake in free living families and the familial aggregation of blood pressure.

A study of 450 men and women is under way in order to determine whether increasing dietary potassium to greater than 120 mEq per day or changing the sodium to potassium ratio to less than or equal to 0.7 will reduce blood pressure. Ongoing investigations are looking

at the effect of weight reduction with or without sodium restriction and moderate potassium increase on blood pressure. Changes in blood pressure will also be evaluated in relation to family history of premature cardiovascular disease mortality and history of hypertension.

Preliminary data collected from Mexican-Americans living in San Antonio indicate that this population has an excess of diabetes and related cardiovascular risk factors, over and above that which can be explained on the basis of their excess obesity. Insulin resistance in this population, along with lifestyle and genetic contributions, to diabetes and CVD will be studied in 4,000 Mexican-American and Anglo men and women.

Available evidence on the epidemiology of diabetes indicates that the phenotypic expression of the genetic determinants of the disease are modified by environmental conditions often associated with changes in diet. If specific dietary nutrients that were independently associated with the onset of diabetes (particularly adult type) could be identified, then strategies to prevent expression of the disease might be developed. One study to explore dietary risk factors for diabetes in women takes advantage of the ongoing prospective cohort study begun in 1976 of 121,964 registered nurses, ages 30-55 years, who are followed every 2 years by a mail questionnaire and appropriate followup to confirm diagnoses. A detailed food frequency questionnaire was obtained on the entire cohort in 1980, and after controlling for family history of diabetes and obesity, the importance of several dietary risk factors for diabetes (simple sugars, complex carbohydrates, fats, fiber, and alcohol) are being assessed. This study will involve stratified and multivariate techniques to quantitate the risk of onset of diabetes and different levels of nutrient intake after controlling for other potentially important risk factors such as age, family history and obesity.

Another study on the role of environmental factors, including psychosocial and cultural, in the etiology and complications of diabetes is under way in Japanese Americans living in Seattle. One aspect of the study includes the examination of type II non-insulin-dependent diabetes, and the relationship of diet composition, chronologic age, biologic age, blood pressure, adiposity, use of alcohol or tobacco, physical activity, glycemic control, serum lipids, lifestyle and social stress to the development of retinopathy, nephropathy and neuropathy.

Investigations are under way on the epidemiological, genetic and longitudinal aspects of osteoarthritis and bone loss among three groups: 1) the participants of the Baltimore Longitudinal study; 2) a sample of normal Guamanian Chamorros; and 3) patients afflicted with amyotrophic lateral sclerosis/parkinsonism dementia complex of Guam.

In order to explain a preliminary finding that thin persons have substantially higher mortality rates than the average persons, an investigation of 45,000 persons is under way in order to determine

whether the thinness-mortality association is an artifact representing weight loss due to illness already present when weight was measured, by analyzing weight earlier in life, weight trends, and health status at the time of weighing. The type of thinness associated with mortality will be characterized both in terms of duration of thinness and body build.

Patterns of eating are being investigated in lean and obese humans in terms of the microstructure of meals, i.e., patterns of chewing and swallowing during a meal, and 24-hour eating patterns or times of meals and snacks, their durations, sizes, and frequency as well as the intermeal intervals. These experiments will make possible the comparison of eating patterns of lean people and a variety of obese people in their natural environments, and will show how they respond to some of the major variables known to affect meals and daily eating patterns. Findings from this research may be helpful to the classification of the obesities, specific recommendations for behavioral control of eating, monitoring of compliance with diet programs, and even the possibility of continuous monitoring and signaling of patients when they eat too fast, too long, or too often.

An epidemiological study of oral health status in adults is under way to investigate the long-term oral health effects of severe dental fluorosis by comparing the oral health of affected adults with that of a comparable group of adults who have consumed optimally fluoridated water since birth.

## APPENDIX G

### STUDIES RELATED TO THE NATIONAL HEALTH AND NUTRITION EXAMINATION SURVEYS: NHANES I FOLLOWUP AND NHANES II





## STUDIES RELATED TO THE NATIONAL HEALTH AND NUTRITION EXAMINATION SURVEYS: NHANES I FOLLOWUP AND NHANES II

The National Health and Nutrition Examination Surveys I and II, conducted from 1971-1974 and 1976-1980, respectively, constitute the largest in-depth national survey of health and nutrition ever conducted on a representative sample of the U.S. population. Participants responded to questions about their nutrition and health history, and received a detailed physical examination, including extensive laboratory tests.

### INITIAL FOLLOWUP OF NHANES I

In 1983, the initial followup of the 14,407 persons ages 25-74 years at the time of the original NHANES I was conducted. The followup originated as a joint project between the National Center for Health Statistics and the National Institute on Aging, but since has received input and financial support from several other Institutes of the NIH.

Over 90 percent of the original NHANES I participants were traced, and of those, the response rate was over 90 percent, yielding a final interview rate of approximately 83 percent. The information collected on the participants included: 1) in-person interviews with the subjects or their proxies; 2) weight and blood pressure measurements; 3) hospital and nursing home records; and 4) death certificates. The collection of hospital patient records is still ongoing.

Many analyses are currently under way using the initial followup 1983 data. A publications committee to coordinate the scientific output from this project has received over 100 abstracts identifying projects to be done using these data. Scientists of NCI, NICHD, NHLBI, NIA, NINCDS and NIADDK are looking at the NHANES dietary data and initial followup study data in order to test a number of hypotheses on the relationship of dietary practices to the incidence of diseases such as cancer, cardiovascular disease, obesity and osteoporosis, as well as diet's effect on overall health and longevity. Some of the Institutes are also collaborating on various projects. Examples of the research proposed and currently supported are given below.

In order to properly utilize the dietary interview information in cohort analyses, the data needs to be formulated into several well defined measures of nutrient intake, food groups, and basic dietary and cooking patterns. For example, measures of the quantity and type of fat consumption, and related food groups and cooking practices (such as beef intake and the frequency of frying foods), as well as measures of processed food and food additive consumption need to be developed. Regression analyses will be done to calculate standardized stratum-specific patterns of fat consumption in different age, race, sex, region, and socioeconomic subgroups. Descriptive data on national cooking practices and the number of meals eaten per day also will be obtained.

The possible relationship of diet and various types of cancer is being examined in a number of studies. Studies of colon cancer are examining its incidence and mortality in relation to nutrition indices including the dietary intake of vitamins C, A and E, cruciferous vegetables, dietary fat and fiber; and bowel function at the time of NHANES I survey. Associations between dietary/bowel function characteristics and colon cancer occurrence are being examined in relation to prior medical conditions (e.g., colitis), ethnicity, depression, and weight and height. Dietary factors, bowel function, medical characteristics and demographic characteristics of subjects at the time of NHANES are also being examined in relation to rectal cancer incidence and mortality.

Other studies are concerned with the relationship of specific food groups to cancer incidence and mortality. For example, fruit and vegetable consumption, and its correlates, carotene, vitamins A and C, and fiber intake, as derived from 24-hour recall and food group frequency questions administered in NHANES I will be examined in terms of mortality and incidence of colorectal, lung, breast, prostate, pancreas, bladder, and skin cancers. Other cancers will be grouped and total cancers will be compared with other causes of death.

The relationship between serum cholesterol measurements and subsequent cancer incidence and mortality will be examined with particular attention paid to malignancies of the lung and large bowel, and to the interval between the cholesterol determination and the event under investigation. Data on residence and source of drinking water will also be analyzed in terms of their association with risk of cancer of the colon, rectum, bladder, and brain. Several mortality studies suggest that contaminants such as trihalomethanes in treated drinking water may be causally related to these cancers.

Studies on the relationship of diet and lung cancer will examine the possible role of micronutrients and macronutrients on incidence and mortality. The micronutrients to be considered include thiamine, riboflavin, vitamins C and E, and the possible protective effects of dietary vitamin A intake. The macronutrients to be examined include the 13 food groups included in the NHANES I frequency questionnaire which includes fruits, vegetables, fats, and fiber. Dietary information from NHANES I, followup dietary information, and urine values will be utilized in the analysis which will also include the examination of age, race, sex, region, education, income, occupation, tobacco and alcohol use, and other medical conditions.

Ingestion of the artificial sweeteners, saccharin and cyclamates, has been linked as a risk factor for bladder and possibly kidney cancer. One study will address the question of artificial sweetener consumption along with tobacco use, occupation and basic demographic data including sex, age, race and residence in relation to cancer incidence and mortality.

Malignant melanoma will be studied in terms of its relationship to consumption of the micronutrients of vitamins A, C and E, thiamine, and riboflavin and the 13 food groups included in the NHANES I di-

etary frequency questionnaire. An attempt will be made to identify risk factors that distinguish patients with melanoma from those NHANES study participants who have not developed melanoma. Of particular interest will be nutrition, skin phenotype, hair color, eye color, complexion, number of nevi, occupation, and social class.

Studies have shown gallstones to be the most important risk factor in gallbladder cancer since both share common epidemiological characteristics including female predominance, ethnic susceptibility, and geographic distribution. Thus, gallstones or their underlying metabolic pattern may play an important role in the pathogenesis of biliary tract tumors. The following variables will be examined in terms of their relationship to the incidence of gallstones: number of pregnancies; demographic characteristics; obesity and nutrition (ponderal index); dietary intake of fat and cholesterol, carbohydrates, and total calories; low fiber diets; serum cholesterol; serum cholesterol lowering diets; exogenous estrogens; history of hospitalization for selected disorders; and history of gallbladder disease. By controlling the risk factors for gallstones, the risk of gallbladder cancer may be reduced.

Studies will be done to investigate the relationships between breast cancer and diet, especially intake of fat, saturated fat, total calories, meat and dairy products, and caffeine and methylxanthines. The interrelationship between diet, breast cancer and anthropometric measures including height, weight, age at menarche, age at menopause and skinfold thicknesses also will be examined. Outcomes will be breast cancer incidence within the cohort, breast cancer mortality within the cohort, and breast cancer prevalence at the time of followup. Another study will examine the relationship of alcohol use to breast cancer risk after adjusting for standard reproductive and medical risk factors.

The role of diet in benign breast disease, which shares certain etiology and epidemiological similarities with breast cancer, will be studied from the dietary data from the NHANES 24-hour dietary recall and the followup interview. Cold and hot beverage consumption including coffee and tea, intake of foods containing methylxanthines, fat, and total calories will be examined in relation to the occurrence of benign breast disease.

Caffeine ingestion has been suggested as a risk factor for cancers of the bladder and pancreas and for other conditions. In order to examine the relationship of coffee and tea consumption to subsequent cancer incidence and mortality, the following variables included in the NHANES followup study will be analyzed: 24-hour dietary recall data, tobacco use, and demographic data including age, sex, race and residence.

Other investigations on cancer that will utilize nutrition information obtained from NHANES will examine the relationship of serum vitamin A ascertained at the NHANES I exam and the subsequent incidence of total and site specific cancers; the relationship of dietary calcium intake to cancer incidence rates and all causes of mortality;



the relationship of hematologic and iron status to cancer incidence and mortality; the relationship of frequency and type of vitamin supplement use to total as well as site specific cancer incidence; the role of dental health as an independent risk factor for cancer, especially cancers of the alimentary tract, and the interaction of diet and dental status; and the relationship of dietary patterns in different occupations or groups of occupation to cancer etiology. Dietary patterns that exist in individuals with different psychological profiles will be assessed since a poor cancer prognosis is believed to be associated with a poor mental health outlook. Such an outlook may be due to a poor diet, e.g., irregular meals with a poor balance of food groups and nutrients. The influence of prior emotional states and personality traits on dietary patterns will also be determined.

The NHANES I vitamin supplement data have been recoded to permit the identification of specific vitamins (A, C, E, etc). Vitamin usage by the following demographic and behavioral characteristics has been described: age, sex, geographic region, marital status, poverty index, education, tobacco and alcohol use, exercise and Quetelet's index. Large differences are observed by both demographic and behavioral characteristics. These data will also be used to describe trends in supplement use.

An epidemiological study is planned to examine the relationship between type of infant milk feeding and serum cholesterol levels of 2,349 U.S. children aged 4-11 years using the NHANES I data. These data contain the only currently available information on both types of infant feeding and serum cholesterol levels for a representative sample of U.S. children. This study offers several advantages over previous studies of infant milk feeding and serum cholesterol levels in childhood: a large heterogeneous sample; inclusion of important confounding factors such as current diet and weight; a broad childhood age span; and generalizability of results to the U.S. population. It has been hypothesized that the high cholesterol content of breast milk sets up homeostatic mechanisms that allow for effective cholesterol metabolism in adult life. Findings from this study will be important for identifying early dietary determinants of childhood serum cholesterol levels.

The NHANES I followup survey data also provide an opportunity to study the distributions of blood pressures, measured by standardized methods at two different ages, for a large sample of the total U.S. noninstitutionalized population. This analysis will provide information on changes in blood pressure for a sample from the population, as well as distributions of blood pressure for elderly persons (over 75 years of age). The analysis of these data will include a review of NHANES I blood pressure measurements and changes in individual measurements over the approximate 10-year period. In the interpretation of the data, related factors such as age, ethnic origin, weight, smoking, and cholesterol will be considered in the study. Also, the question of whether these factors, which have been shown to be related to blood pressure level for persons under 65 years of age, are also associated factors for the elderly will be studied. Health status, including cardiovascular and cerebrovascular disease, will be con-

trolled in the analysis. Differences among treated and untreated hypertension will also be examined.

In the area of coronary heart disease, investigators plan to study the relationship of the development of elevated blood pressure and the incidence of coronary heart disease to the inorganic constituents of drinking water. The variables to be analyzed include drinking water hardness, sodium and other constituents, baseline and follow-up blood pressure, initial serum cholesterol values, height, weight, cigarette smoking levels, and new cases of and deaths from coronary heart disease. These blood pressure studies will control for height, weight, and other major covariables.

Another study of hypertension incidence and mortality from coronary heart disease, stroke, etc., will examine the incidence rates of hypertension within quintiles of calcium intake in individuals free from hypertension at baseline (blood pressure under 160/95 mm Hg) and not under medication for hypertension. Age, sex, and race specific rates will also be calculated. Possible confounding due to baseline serum magnesium, potassium, and calcium levels will be investigated. Similar analyses will be conducted for all cause mortality and cause specific mortality from coronary heart disease, stroke and cardiovascular disease.

Data from the NHANES followup survey will be analyzed to assess the effects of three different obesity measures calculated during NHANES I, i.e., relative weight, body mass index, and subscapular skinfolds, on cardiovascular disease among men and women at different ages (50 years, and over 50 years). Regression analyses will adjust for the influence of other cardiovascular risk factors at baseline (NHANES I) including age, cigarette smoking, depression, systolic blood pressure, total cholesterol, glucose intolerance (diabetes, positive urine sugar) and left ventricular hypertrophy on electrocardiogram. End points of specific interest are coronary heart disease, congestive heart failure, and stroke morbidity and mortality.

Conflicting evidence exists on the effects of prescribed estrogen therapy used for the prevention of osteoporosis in terms of its effects on cardiovascular morbidity and mortality. A regression model will be used to assess the effects of therapeutic estrogen/ progesterone use in postmenopausal women in NHANES I. Adjustments will be made for other cardiovascular disease risk factors such as cigarette smoking, relative weight, systolic blood pressure, total serum cholesterol, and glucose intolerance. Concurrent use of estrogen/progesterone with cardiovascular disease in NHANES followup will also be examined.

Another study will examine the concurrent interactive effects of estrogen use, smoking, and obesity on age at menopause from data obtained from the NHANES I and the NHANES followup survey since several studies have reported a relationship between heavy smoking and early menopause, whereas obesity has been associated with later menopause. Smoking is negatively associated with obesity, and studies to date have not determined which factor is more predictive of early

menopause in nonobese women who smoke. A methodological study using the NHANES population will compare various indices of body mass as they relate to morbidity and mortality. The analyses will incorporate physician's perception of obesity and anthropometric measurements from the NHANES I (i.e., weight, height, skinfold thickness) and followup surveys of weight. Age and sex-specific comparisons will be examined, and indices that would be favorable for studying conditions of the elderly will be determined.

The study of the importance of weight and weight corrected for height (body mass index) as predictors of morbidity and mortality includes indicators of weight obtained in the original NHANES I (body weight, skinfold thickness, physicians's evaluation of obesity), as well as measurements of weight and questions pertaining to weight history in the followup survey. The study will relate distributions of weight and body mass, changes in weight and weight history to health status, and health outcomes of the participants.

Additional studies of the elderly will look at food consumption in the original NHANES I and followup survey in order to define dietary patterns of elderly persons and changes in dietary patterns with age and relate these patterns to morbidity, disability, and mortality. Emphasis will be on total calories, fat, protein, carbohydrates, and possibly vitamins and minerals. This analysis will provide a general overview of the relationship between dietary and nutritional histories and medically definable outcomes in the elderly. Another study will attempt to define the characteristics most commonly found among usually healthy older persons, and the factors or characteristics which predict longevity and good health in later life. Those variables to be examined for possible association with good health will be drawn from both the original and followup contact and include age, sex, initial blood pressure, diet/nutrition, physical activity, alcohol and smoking, anthropometric measures and weight history, among others.

Another study will examine possible associations between hip fracture occurrence and various factors at original contact and at followup including socioeconomic status (education, income, work), and histories of height and weight, diet, menopause, estrogen use, smoking, alcohol use, activity, and blood pressure thiazide use.

Diet and nutrition information will also be examined as one of the variables associated with performance of older persons on the mental health status questionnaire. Age and other demographic or personal characteristics, depression, physical activity, functional disability, etc., will also be considered in order to develop an understanding of the correlates and risk factors that may influence performance. Personality correlates of those variables already identified as having an impact on disease, such as nutrition and weight, alcohol use, smoking, physical activity, and openness to experience, will also be studied.

The use of vitamin supplements and nonprescription medications of older individuals will be related to health self-assessment using data



from the NHANES I and NHANES followup survey by investigating the following four questions: 1) Does health self-assessment differ as a function of the use of vitamin supplements or nonprescription medications, and are these differences related to demographic characteristics such as age, sex, ethnicity? 2) Are personality variables related to the use of nonprescription medications or vitamin supplements? 3) Does objective health (as measured by reported physician's diagnoses and hospitalizations) differ as a function of the use of vitamin supplements or nonprescription medications and are these differences related to demographic characteristics? 4) Are changes in self-medication related to changes in health self-assessments over the 10-year followup interval?

#### CONTINUED FOLLOWUP OF NHANES I

In addition to the studies of the initial followup of NHANES I data, the concept of a continued followup of NHANES I was approved by the NCI Board of Scientific Counselors in May 1984. The purpose of the continued followup study is to investigate the relationship of physiological, environmental, nutritional, social, psychological, and demographic factors to morbidity and mortality from specific diseases, as well as hospitalization and nursing home utilization. More specifically, the objectives of this study are: 1) to identify chronic disease risk factors associated with morbidity and mortality; 2) to ascertain changes in risk factors, morbidity, functional limitation and institutionalization between NHANES I and the recontacts; and 3) to map the natural history of chronic diseases and functional impairments in an aging population. Clues to cancer etiology learned from the study of this cohort will provide a valuable basis for the effective planning of future intervention strategies.

The continued followup will extend the period of observation of this cohort by an additional 5 years. Telephone contact will be made annually with individuals over 75 years of age and biannually for those under 75 years, at which time an interview questionnaire will be completed requesting information on functional impairments, hospitalizations, and changes in health status or work status. For the approximately 1,000 NHANES I participants not contacted in the 1983 initial followup, information for subsequent tracing will be asked. Medical record information for hospitalizations will be sought to validate respondent reporting. The National Death Index (NDI), state vital statistic sources, and Social Security death files will be used to establish vital status. The continued followup will be managed and funded in a fashion similar to the initial followup. NCHS will direct the contract and financial support is anticipated from a number of Institutes including NIA, NIADDK, NHLBI, and the National Institute of Alcohol Abuse and Alcoholism (NIAAA) and the National Institute of Mental Health (NIMH) of the Alcohol, Drug Abuse and Mental Health Administration (ADAMHA).



## NHANES II

The NCI's Division of Cancer Prevention and Control also plans to analyze the raw data files of the NHANES II survey and create a profile of the major cancer risk factors, i.e., smoking, diet, and occupation. In addition to the multiple risk factor analysis, the investigators plan to examine the major risk factors separately, as appropriate, as well as particular pairs of risk factors, and to create a data base which may be useful to other disease-oriented investigators, especially those related to heart disease. The NCI projects that involve investigations using the dietary data set of NHANES II are described below.

The NHANES II dietary data have been used to develop a database dietary assessment questionnaire, i.e., to identify foods that should be included in the questionnaire in order to adequately assess calories and 17 major nutrients. They were also used to determine age and sex specific portion sizes to be used in the nutrient calculations. The questionnaire and its associated nutrient analysis program are currently in use, and produce nutrient estimates well correlated with values found in national surveys.

The dietary data have been used to provide quantitative information on the important sources of 18 nutrients in the U.S. diet. For each of the nutrients, food lists were ranked by the percent of total U.S. intake that each food provided. These data will be useful to researchers developing dietary assessment instruments, and to public health policymakers and educators. These data reveal, for example, that 27 percent of all the vitamin C consumed in the U.S. diet comes from orange juice; that 4 percent of all the provitamin A comes from vegetable soups; and that 15 percent of all the fat in the diet comes from beef.

The dietary data have been used to identify the important nutrient contributors by demographic subgroups. These analyses reveal quantitative information on generational and racial differences in preferred nutrient sources. For example, fortified fruit drinks are the second most important sources of vitamin C for the young, but are much less important for older groups. Similarly, greens such as collard and kale are trivial sources of vitamin C for whites, but major sources, ranking as high as second, for blacks.

The population's consumption of and sources of total dietary fiber and folate will be described using the NHANES II dietary data since the latest information on fiber and folate values have been added to the data set. Demographic subgroup specific tables of food sources of fiber--in terms of total population contributions, not just nutrient composition--will be developed.

## **APPENDIX H**

### **DESCRIPTION OF RFA's, RFP's, and PA's IN NUTRITION RESEARCH**



## DESCRIPTION OF RFA's, RFP's, and PA's IN NUTRITION RESEARCH

The RFA, "Specialized Caries Research Centers," issued by NIDR, solicited applications for the support of centers to conduct multidisciplinary, fundamental and clinical research on the etiology, pathogenesis and prevention of dental caries. Dental caries affects the majority of people and it is the leading cause of tooth loss in children and young adults. Recent surveys indicate that the prevalence of coronal caries among children has decreased during the last decade probably because of the widespread application of fluorides. However, two-thirds of the nation's school children suffer from the disease. Very little is known about secondary caries and root caries, which affects adults and may be increasing in prevalence, therefore additional research is needed. Each center will be an identifiable unit which will consist of a cluster of related research projects, some of which will be fundamental and others will involve clinical studies. The research projects will focus on the following four strategy areas: combating the responsible microbiological agents, increasing the resistance of the tooth and the host, decreasing the caries conducive properties of the diet, and improving the delivery and acceptance of caries preventive methods. It is anticipated that the centers will encourage research collaboration and will provide a training environment for young investigators.

The RFA, "Cardiovascular Disease Prevention in the Workplace," issued by NHLBI, sought applications to support demonstration and education research in cardiovascular disease prevention and health promotion in the workplace. Efforts to implement workplace high blood pressure control programs have been successful in achieving improved high blood pressure control. Other cardiovascular risk factors such as smoking cessation, physical fitness, and weight control also need to be addressed in health promotion/disease prevention programs. Standardized methods to assess the clinical and behavioral effectiveness of cardiovascular disease risk factor reduction programs will be developed and implemented in the workplace, and standardized cost effectiveness and cost benefit analysis of the program will be carried out. Nutrition will be an important element of the risk factor intervention efforts. Assessment of need should include questions on nutrition knowledge about risk factors, per se. Appropriate methods for achieving and maintaining long-term dietary changes in this setting will also be investigated, along with dietary adherence measures such as weight change, anthropometric measures, food record ratings, etc. Assessment of outside influences and activities may be critical to achieving appropriate dietary outcomes. Family food habits may enhance or impede nutrition intervention efforts at the workplace. The familial nature of most of the CVD risk factors gives strong support to the need for involvement of family members in risk reduction programs.

The RFA, "Sodium Sensitivity and Blood Pressure Response," issued by NHLBI, solicited applications to identify the mechanisms and characteristics that determine sodium sensitivity and resulting blood pressure changes in normotensives and in persons with essential



hypertension. Evidence exists to support the contention that certain persons with essential hypertension respond differently to a high sodium intake than those who are normotensive or who are "non-sodium" sensitive. Among the findings reported with salt loading in sodium sensitive hypertensives are sodium and water retention, increase in body weight, lower rates of urinary excretion of sodium, and increase in blood pressure--as contrasted to other persons who have essential hypertension but are not responsive to sodium loads. With sodium restriction, these same "sodium sensitive" individuals may also have relatively low rates of urinary excretion of aldosterone. Tests, biologic responses, or markers that may predict those persons who would respond to sodium restriction for the treatment of hypertension are needed. Preventive measures and therapy, pharmacologic or non-pharmacologic measures could then be initiated with better scientific justification and with greater efficiency. Applications that study both normal and hypertensive persons are preferred to those which study only persons with normal blood pressure.

The RFP, "Support of Analysis of LRC Program Clinical and Epidemiological Data Sets," issued by NHLBI, sought proposals for a limited competition among Lipid Research Clinics (LRC) investigators to participate in the analysis of data from the LRC Population Studies (Prevalence, Family, and Mortality Follow-up Studies) and the Coronary Primary Prevention Trial (CPPT). The LRC Prevalence Study has provided information on the distribution of lipids and lipoproteins in diverse well-defined North American populations, i.e., analysis of the data has described changes in lipid and lipoprotein levels associated with estrogen use in women, the effects of alcohol intake and smoking on blood pressure and lipid and lipoprotein levels, the relationship of nutrient intake to high density lipoprotein levels, as well as age, sex, and race differences in lipid levels and associated risk factors. The Family Study is a unique data set of over 2,400 families for the study of environmental and genetic etiologies of dyslipoproteinemia. The Mortality Follow-Up Study provides valuable information on the association of coronary heart disease risk factors including high density lipoproteins and triglyceride levels, estrogen use, and subsequent mortality in the LRC Prevalence populations. The relationship of nutritional and electrocardiographic factors to mortality is being considered as is the study of lipoprotein levels, retinol levels and estrogen use (in women) to cancer mortality. Data collected in the LRC-CPPT will be evaluated in terms of the efficacy of diet and/or drug intervention among different risk or treatment groups, and will have implications for medical care practice or the design of public health strategies for the general population and studies of the natural history of CHD and associated risk factors within high risk groups. The LRC data sets represent an extensive and invaluable biomedical resource for the study of cardiovascular disease and associated risk factors such as lipid and lipoprotein levels, blood pressure, smoking, dietary factors, physical characteristics and socioeconomic attributes.

The RFA, "National Research and Demonstration Centers and Specialized Centers of Research in Hypertension," issued by NHLBI, sought applications in hypertension research that span the biomedical research

spectrum including basic science, clinical research, and demonstration and education research. The new National Research and Demonstration Centers (NRDC) program is envisioned as an enhancement of the Institute's Hypertension Specialized Centers of Research (H-SCOR) program through the addition of a thematically related component in demonstration and education research. The NRDC's must include the following essential elements: an H-SCOR, encompassing both basic (laboratory-based) research and clinical investigation; demonstration and education research; and an organizational unit for coordination, integration and evaluation of the entire spectrum of essential elements listed above. The basic research and clinical investigation component of the NRDC will include research on the many factors associated with blood pressure regulation ranging from the genetic to environmental. Studies have shown that in cases of sodium-induced hypertension, the restriction of sodium does indeed lower blood pressure, however, more research is needed to identify the sodium sensitive individual. The roles of dietary fat restriction, potassium and calcium supplementation, and exercise and relaxation techniques in the prevention of hypertension need to be clarified. The demonstration and education research component of the NRDC involves testing of the effectiveness of interventions to promote health or prevent disease in defined populations.

The RFP, "Efficacy Studies of Chemopreventive Agents in Animal Models Including Synthesis, Bioavailability and Encapsulation Studies," issued by NCI, sought proposals to evaluate the efficacy of various designated chemopreventive agents at several dose levels in animal models and the refinement and improvement of animal test models for chemopreventive studies. The project will also involve synthesis, bioavailability and encapsulation studies for selected agents such as retinoids (vitamin A, retinoic acid, retinyl methyl ether), antioxidants (phenols, isothiocyanates), dietary factors (fiber, garlic), essential trace minerals (selenium, copper, zinc), other vitamins, provitamins or cofactors (vitamins C and E, riboflavin). The emphasis of this activity is to take initial leads on designated agents and expand the data base as to the spectrum of carcinogens, spectrum of target sites, and ranges of species.

The PA, "Biobehavioral Sequelae of Antihypertensive Therapies," issued by NHLBI, encouraged applications for research to identify potential cognitive and/or behavioral sequelae resulting from pharmacologic and nonpharmacologic treatments to lower blood pressure. Several issues that require additional study include determination of the level of blood pressure to initiate pharmacologic therapy, the efficacy of nonpharmacologic therapies in their various forms, and whether children, adolescents and the elderly should be included in therapy programs. Controlled studies that involve nonpharmacologic therapies or combinations of pharmacologic and nonpharmacologic regimens are particularly pertinent to this announcement. Diet/weight reduction, exercise, and relaxation/biofeedback therapies, singly or in combination with each other and/or pharmacologic regimens are examples of treatment approaches that could be assessed in terms of behavioral and cognitive deficit or improvements associated with changes in blood pressure. Investigation of interaction effects of such demographic

variables such as age, sex, diet, family history, severity and duration of hypertension, and smoking history is also encouraged.

The PA, "Special Emphasis Research Career Award for Social and Behavioral Scientists in Geriatrics Research," issued by NIA, sought applications from investigators who have appropriate training and experience to design and conduct interdisciplinary research on health behaviors and aging, who can define the common ground between psychosocial and biomedical approaches, and who can speak each other's scientific language. This need for geriatric researchers with biobehavioral backgrounds will predictably increase as both social/behavioral and geriatric research programs develop in schools of medicine and public health, in behaviorally oriented biological and medical research laboratories and in the wide range of institutions and agencies concerned with science-based health care of older persons. During the first year or two, the awardee is expected to develop capabilities for conducting interdisciplinary research on aging and health promotion in a clinical or other biomedical setting. The awardee should be exposed to at least one biomedical speciality, such as general or geriatric medicine, nutrition, immunology, neurology, neuroendocrinology, or pharmacology. Activities should be oriented around an area of research in behavioral geriatrics.

The RFA, "A Phase III Trial of a Low Fat Diet in Women at Increased Risk for Breast Cancer," issued by NCI, solicited applications for cooperative agreements to support participation in a multi-institutional randomized clinical trial of a low fat diet (20 percent of calories) aimed at reducing the incidence of breast cancer in women at increased risk for breast cancer. Participants will be funded in one or all three of the following categories: clinical units, nutritional coordinating units, and statistical coordinating units. The trial will be initiated in three stages (protocol writing, feasibility, and full implementation). Specific items relevant to applications from the nutrition coordinating units are as follows: the applicant should propose an initial course of instruction for the nutritionists from the participating clinical units, including written instructional materials and a workshop; discuss the development of food shopping plans, menus, recipes, etc. to be used by study participants; and discuss and describe plans to convert dietary data into nutrient content with a maximum of a 2-week turn around; and should discuss plans for quality control on all phases of dietary monitoring.

The RFP, "Phase I Studies of New Chemopreventive Agents," issued by NCI, sought proposals to determine, in humans, the parameters and characteristics of toxicity, the maximally tolerated or safely delivered dose, and the basic clinical pharmacokinetics of agents emerging from the NCI chemopreventive agent development program.

The RFP, "A Case Control Study of Vitamin Supplementation and Neural Tube Defects," issued by NICHD, solicited proposals for a collaborative study of the efficacy of vitamin/folate supplementation around the time of conception in the prevention of neural tube defects. Several lines of evidence suggest a relationship between vitamin/folate levels and neural tube defect rates. Recent studies have



suggested that periconceptional vitamin/folate use may prevent these serious malformations. If validated, these findings have major implications for women hoping to become pregnant. The proposed study will identify children who have been born recently with neural tube defects and appropriate controls. Mothers will be contacted by telephone and asked retrospectively about vitamin use, which many American women use on a regular basis.

The RFP, "Data Coordinating Center for a Case Control Study of Vitamin Supplementation and Neural Tube Defects," issued by NICHD, sought proposals from organizations capable of providing the services of a Data Coordinating Center for the proposed multicenter case control study of vitamin supplementation and neural tube defects. The functions of the proposed data center include the following: receiving data from the study centers, checking the data, coding for computer entry, entering the data onto a computer file, monitoring the quality of the data submitted, and analysis of the data. The data coordinating center is necessary to ensure the quality and accuracy of the data collected; it will assist in the analysis of the data and the data will be communicated frequently and directly to the project officer and the study centers. The purpose of the contract is to determine whether the use of vitamin/folate supplements around the time of conception reduces the risk of producing an infant with neural tube defects.

The RFP, "International Food Composition Data System," issued by NCI, sought proposals to develop and implement an international food data system which will facilitate the transfer of reliable food data within and between countries. Information on the nutrient and the nonnutrient composition of foods, beverages and their ingredients contributes significantly to a variety of research and service activities. These range from the assessment of population intake of nutrients and nonnutrient food constituents to the formulation of food production and nutrition policies and programs, and to institutional meal planning and calculation of therapeutic diets. Furthermore, increasing interest in and concern for the relationships between diet, food habits and degenerative diseases, including coronary heart disease, diabetes, hypertension, stroke and cancers has stimulated a current interest in detailed chemical data on foods. The establishment of an International Food Composition System would enhance the quality, quantity and accessibility of nutrient and nonnutrient data. These data will give reliable representative data for indigenous foods, and whenever possible, reflect the effect of growing conditions and treatments before consumption. Thus, comprehensive studies of nutrient or other components in foodstuffs, including contaminants, toxic substances and nonnutritive chemicals, could be undertaken. This data system is of particular importance to NCI since the assessment of the dietary intake of various food components is basic to many of the current and planned epidemiological studies and intervention trials.

The RFA, "Biochemical Epidemiology," issued by NCI, sought applications for investigations to stimulate the development and/or use of objective measures of risk in epidemiological studies of the etiology



of human cancer. The process of induction and progression of human cancer is exceedingly complex: multiple exposure to a variety of agents over time is the rule rather than the exception, past exposure is difficult to assess, host factors which may influence susceptibility are poorly understood, and the importance of promoting anticarcinogenic exposures in humans have not been adequately defined. Epidemiologic studies have resulted in the identification of factors which appear to increase or decrease cancer risk and have suggested the importance of host-susceptibility factors. Modifying factors related to diet and cancer have been implicated in several epithelial cancers including those of the gastrointestinal tract and reproductive organs. Hence, these types of cancers (among others) might be especially suitable for collaborative studies involving epidemiologists and experimentalists.

The RFA, "The Role of Micro and Macronutrients in the Prevention of Cancer," issued by NCI, sought applications for cooperative agreements to support risk reduction clinical trials to study the effect of micro and macronutrients on cancer risk in humans. The micronutrients include but are not limited to the following: beta carotene, vitamin A or analogues, vitamin C, selenium, and alpha tocopherol. In addition, intervention trials involving several macronutrients including fats, vegetables, fruits, cereals, and fibers will be considered. Clinical intervention studies are now being encouraged because of the numerous reports concerning the effectiveness of dietary manipulation or the administration of certain compounds in interfering with carcinogenesis in animals, and the many epidemiological studies that suggest a possible negative association of certain dietary factors with cancer incidence. The studies of interest are risk reduction clinical trials involving normal populations, populations known to be at increased risk but free of neoplasia, or high risk populations with identified precursor or precancerous lesions.

The RFP, "Methodology and Analysis of Fiber Components in Food," issued by NCI, solicited proposals to develop new or improve existing methodologies for the determination of total dietary fiber as well as for the separation, identification and quantitation of different fiber fractions. Appropriate standard reference materials and/or quality control samples need to be secured or developed for data validation. Methods of extraction of total dietary fiber and fiber fractions from different food matrixes need to be developed which preserve the stable/unstable species and remove interfering compounds. To apply the analytical methodologies to determine the fiber content of foods, selection of food samples becomes an important issue. Strategies to select important food items in the food supply and secure a representative sample of these items will be developed. Important food items include those which contribute a major portion of fibers in the U.S. food supply. Furthermore, data concerning the effects of processing on the various fiber components will be assessed to provide analytical values for foods consumed. The procurement is expected to result in a reliable data base of total dietary fiber and fiber fractions to be used in dietary assessment/prevention studies of the NCI.

The RFA, "Data Coordinating Center for Cooperative Clinical Study of Dietary Modification on the Course of Progressive Renal Disease," issued by NIADDK, sought cooperative agreement applications from organizations to serve as a data coordinating center in a multicenter cooperative clinical study seeking to define the influence of controlled nutritional intervention on the progression of chronic renal disease/renal insufficiency. Some evidence from animal investigations and clinical observations in humans suggest that dietary restriction exerts a favorable effect on the rate of progression of several chronic renal diseases. These observations form the basis for the following hypothesis to be tested in the proposed clinical studies: 1) restriction of dietary protein reduces the rate of progress of chronic renal disease in humans; and 2) dietary protein restriction is nutritionally safe (if effective) in patients with progressive renal failure. The primary question to be addressed by this study relates to the effect of empiric dietary restriction of protein on the rate of progression of renal failure. Ascertainment of the effects of such intervention would also indicate whether the need for maintenance dialysis therapy can be delayed and thereby reduced by dietary manipulation.

The RFP, "NHLBI Nutrition Data System," issued by NHLBI, sought proposals for the preservation and enhancement of the NHLBI nutrition data system and its components; its continued availability to the NHLBI as well as to others in the scientific community; and the establishment of a central, self-sustaining resource encompassing these capabilities. The nutrition data system was first established in order to facilitate the standardized collection and processing of the dietary intake data collected as part of the two collaborative research programs, the Lipid Research Clinics (LRC) and the Multiple Risk Factor Intervention Trial (MRFIT). Although the data collection phase of the LRC and MRFIT has ended, analysis of the data will continue and new hypotheses will be tested regarding the role of different nutrients and nutrient interactions in lipid metabolism and coronary heart disease. In order to meet these demands the nutrient data base must be kept current. There will be a need for a nutrition coding center both to assure the maintenance of the integrity of all aspects of the Table of Food Composition, and to permit access to new nutrient data during the analysis phase of the studies. An important long-range goal of the center would be to serve as a resource to the broader scientific community in providing nutrition data and in addressing the issues surrounding quality control in nutrition data collection and processing. A single ongoing facility that can provide and maintain a comprehensive nutrient data base and a standardized system for the collection and processing of dietary information is envisioned, yielding the most current information and reflecting state-of-the art technology.

The RFA, "Perinatal Emphasis Research Center - Perinatal Pharmacology and Toxicology," issued by NICHD, solicited applications for a Perinatal Emphasis Research Center (PERC) to promote and support multidisciplinary research efforts in areas where knowledge gaps are not being sufficiently addressed by ongoing research or there are needs to stimulate and intensify efforts in promising research areas. PERC's

are located throughout the United States and presently are addressing issues in high risk pregnancies (diabetes, hypertension), prevention of prematurity, and fetal hypoxia. This proposed PERC will deal with the impact of drugs and chemicals, in vivo and/or in vitro, on maternal, fetal and neonatal tissues. Investigators are invited to propose studies including neonatal pharmacology, general toxicology, and teratogenesis in both humans and experimental animals. The role of genetic composition, nutrition, duration and stage of gestation, presence of acquired disease in mother and/or developing fetus, and other factors on drug disposition and effect are of interest.

The RFA, "National Research Service Awards for Institutional, Postdoctoral Training Programs in Caries Research," issued by NIDR, sought applications from U.S. organizations to provide postdoctoral training in caries research. Trainees will be provided with didactic instruction in dental and oral anatomy and physiology, composition and functions of saliva, microbial and dietary factors in caries etiology, use of animal models in caries research, principles of epidemiology and biostatistics, and the design and conduct of clinical trials. The progressive tooth destruction characteristic of dental caries results from the interactions among three primary factors: oral bacteria, capable of fermenting dietary substrates to produce acid, which dissolves the tooth enamel of a susceptible host. Investigation of the diverse factors implicated in caries etiology and the development and evaluation of preventive measures necessitates participation by investigators from numerous disciplines including chemists, microbiologists, nutritionists, pharmacologists, statisticians, dentists, etc. experienced in conducting clinical trials and demonstration programs.

The PA, "The NCI Clinical Investigator Award," issued by NCI, solicited applications for the purpose of developing physician-researchers in basic and applied cancer sciences. The award was prompted by the chronic shortage of physician-investigators, particularly surgical oncologists, therapeutic radiologists, diagnostic radiologists, nutritionists, preventive oncologists, psychiatrists, and epidemiologists. The award will enable successful candidates to investigate for up to 3 years a defined cancer problem under the guidance of an active researcher who has the knowledge, background, and research experience required to be a mentor in that field.

The RFP, "Investigations of Cervical Cancer in Latin America," issued by NCI sought proposals to identify characteristics of Latin American women that are predictive of risk of developing invasive cervical cancer; to identify behavioral characteristics of Latin males that may contribute to the high rates of cervical cancer; and to relate certain biochemical indicators (e.g., infectious agents, micronutrients) as measured in both males and females to risk of cervical cancer. Cancer registries in a number of Latin American countries document the world's highest incidence rates whereby invasive cervical cancer equals about half of all male cancers combined.

The RFP, "Prospective Physiological and Psychological Follow-up of Offspring of Diabetic Mothers", issued by NICHD, sought proposals to



assess the long-range physiological and psychological development of offspring of diabetic mothers whose pregnancies have been monitored prospectively in regard to carbohydrate, lipid, and amino acid metabolism. The reason for initiating a longitudinal followup of infants of carefully documented diabetic pregnancies is to ascertain whether the altered intrauterine metabolic environment of these pregnancies causes significant permanent deviations from normal physiological and psychological development. The goal of the study is to discern possible functional impairments in childhood engendered by metabolic deviations from normal in-utero environment.

The RFP, "Oral Contraceptives, Folate and Cervical Dysplasia," issued by NICHD, sought proposals for the performance of the first phase of a two-phase project to evaluate the relationship between oral contraceptive use and the occurrence of cervical dysplasia with an emphasis on investigating the hypothesis that folate status may have an important influence on this relationship. The proposed project has the following two related objectives: a case-control study to investigate the relationship between oral contraceptive use, nutritional folate status, and the occurrence of cervical dysplasia; and a randomized clinical trial to evaluate the efficacy of therapy with monoglutamic folate for halting the progression of, or reversing, cervical dysplasia in oral contraceptive users as compared to nonusers. The results of the proposed project should help to establish whether there is a rational basis for recommending that women using oral contraceptives should be periodically screened for low folate status and/or be advised to supplement their intake of folate.

The PA, "Basic Mechanisms of Retinal Phototoxicity," issued by NEI, sought applications to encourage research which seeks to understand the basic mechanisms of how the metabolic status of the retina influences the susceptibility of photoreceptor cells to damage by light energy. It is important to differentiate between the way in which intrinsic factors (metabolic and nutritional) and extrinsic factors (light energy) may contribute to aging, retinal degeneration, and macular degeneration. Some of the program development priorities related to this announcement include examination of the effects of light, age, drugs, and antioxidants on lipofuscin; investigation of environmental and nutrition factors affecting photoreceptor function, degeneration and aging; and studies on retinal metabolism and biochemical processes critical to retinal function. Photoreceptor cells contain vitamin E as well as several other antioxidants such as selenium which may function in a protective capacity to prevent buildup of toxic molecules. Nutritional deficiencies that deplete vitamins A and E, taurine, selenium and zinc may cause photoreceptor degeneration, but the mechanisms are unclear and need to be investigated.

The joint PA, "Studies on Obesity," issued by NIADDK, NCI, NHLBI, NIA, NICHD, NINCDS, NIAAA, NIDA and NIMH, sought applications for the support of research on the biomedical and behavioral aspects of exogenous obesity. The goals of this research, which includes both basic and clinical research, are to establish a clear understanding of the etiology, prevention, and treatment of this multifaceted condition. For example, the determinants of obesity during the early



stages of the life cycle need to be identified in order to prevent the onset of obesity early in life and to identify individuals at high risk of becoming obese later in life. The question of whether obesity is a risk factor per se for the development of other disease states needs to be clarified, as well as its relationship to mortality. Preventive therapies along with successful treatment regimens need to be designed. In order to accomplish these goals, further research is needed on the behavioral and developmental aspects of obesity in terms of its natural history and determinants in infancy, childhood, and adolescence; on the metabolic, genetic and neurological aspects of obesity; on the successful treatment of overnutrition and obesity; and on the effects of obesity on body weight, health, and longevity.

The RFA, "Obesity and Cancer Risk in Women," issued by NCI, sought applications to stimulate research to elucidate the nature of the association between obesity and cancer risk in women, including the development of new research methods which may enhance the understanding of pertinent metabolic processes or improve the measurement of informative parameters. Research questions of interest include, but are not limited to the following: Is the association causal, if not what other factors might explain the observed associations between obesity and increased risk of certain cancers; is the association with obesity related to certain forms of body fat distribution; is the association explained by the conversion of adrenal hormones to estrogen, or are more complex metabolic, hormonal or enzymatic processes involved; how do diet and physical activity relate to obesity and cancer risk; what parameters are informative for studies of obesity and cancer risk and how can their measurement be improved; is the mobilization of fat associated with cancer risk either in association with lactation, weight loss, or change in hormonal status; and how do individuals differ in the conversion of dietary constituents to adipose tissue and how do these differences relate to cancer risk.

The RFP, "Nutrition Intervention Trial in Linxian, China," issued by NCI, sought applications for a nutrition intervention trial to determine whether there is a relationship between esophageal cancer in Linxian, China, where the incidence rates of this type of malignancy are the highest in the world, and chronic nutritional deficiencies which are endemic to the area. Vitamin/mineral supplements will be evaluated in terms of their etiologic role in reducing esophageal cancer rates in a population of approximately 30,000 adults, ages 40 to 69 years, from Linxian's northern communes, with at least 3,000 persons having recently diagnosed severe dysplasia of the esophagus. A nutrition surveillance program will be conducted to monitor secular and seasonal changes in the diet during the course of the study and changes in nutritional status between treatment groups. A brief dietary interview will be used prior to the start of taking the supplements and seasonally during the course of the trial. Laboratory analysis will be carried out on the nutritional status of the fat soluble and water soluble vitamins, trace elements, and possibly protein. Gross seasonal and study period data will be collected on food production and distribution as well as other measures that indicate the nature of the food supply. Changes in the cytologic gradings of esophageal cells will be assessed according to supplement usage in the treatment group.

The RFA, "Dietary Markers for Epidemiologic Studies of Cancer," issued by NCI, solicited applications to encourage investigations designed to identify, characterize and validate markers of present or past dietary exposure which could be useful in the validation or the conduct of nutritionally focused studies in cancer epidemiology. Such factors as ease of conduct and expense as well as collection, storage, and transport problems should be considered along with the accuracy and validity of the method. The range of materials for which markers of exposure are of interest is extremely diverse. Included would be any foods and beverages, food groups or components, nutrients or trace elements derived from dietary sources which have been proposed to alter the risk of malignancy and for which human exposure is likely to have occurred. The current emphasis on nutritional factors as modulators of carcinogenesis in human populations has created an increased awareness of the need for biologic markers of present and past dietary exposures that might alter cancer risk. Experimental animal studies have indicated that the intake of specific dietary components is an important determinant of cancer risk. Attempts to apply these findings to the human situation are hindered by the difficulty of classifying individuals into intake (or exposure) categories. It would clearly be advantageous to have available biochemical measures (preferably minimally invasive) which would provide unambiguous markers of the level and distribution of the dietary constituents in individuals. Such methodology would facilitate the design, conduct, and interpretation of epidemiologic studies focused on the relationship between diet, nutrition and cancer risk.

The RFA, "Rat Pancreatic Exocrine Lesions: Biological Nature and Possible Role of Vegetable Oil in Formation of These Lesions in Gavage Studies," issued by NIEHS, sought cooperative agreement applications from institutions or research groups capable and interested in defining the relationship of dietary oil and increased incidence of pancreatic acinar cell proliferative lesions found in rats. A means to provide an accepted classification scheme of rat proliferative exocrine pancreatic lesions based on the biological nature of the lesions is also considered important. Pancreatic cancer is the fourth leading cause of cancer death in the U.S and appears to be increasing. Several studies have shown that dietary oils can significantly enhance the incidence of proliferative pancreatic lesions in rodent models. This effect is modulated by the amount of oil, type of oil (types or fatty acids may be important), level of saturation, and temporal relationship between carcinogen and oil exposure. Investigators have also shown that dietary fat and protein levels affect the incidence and onset of a variety of cancers.

The RFP, "Evaluation of Chemopreventive Agents by In Vivo Screening Assays," issued by NCI, sought proposals for studies to evaluate inhibitors of carcinogenesis by various designated chemopreventive agents in short term in vivo screening assays. These studies will evaluate and qualify certain chemopreventive agents so that evaluation of dose response and target tissue specificity can be done in longer term efficacy studies having relevance to human cancer. The studies will monitor tumorigenesis, body weight, and clinical appear-

ance. The results of these *in vivo* screening experiments will be used to select promising chemoprevention agents for other planned studies whose objectives are to study the dose response of the chemoprevention agent, its spectrum of anticarcinogenic activity, its spectrum of target sites, and the species in which it is active. These agents will then be considered for toxicology evaluation and for their possible use in human clinical trials. Cancer chemoprevention is aimed at testing the concept that certain natural or synthetic agents may lower cancer incidence. Potential chemopreventive agents include several naturally occurring substances already in public use, such as vitamin A and its precursor beta-carotene, ascorbic acid (vitamin C), alpha-tocopherol (vitamin E) and selenium as well as others still in the realm of the laboratory such as antioxidants, phenolic, protease, and prostaglandin synthesis inhibitors, tumor growth factor inhibitors, secondary plant constituents, and miscellaneous chemicals (e.g. asparagine and uric acid). Retinoids have been actively investigated for their anticarcinogenic potential. Human trials in cancer prevention are underway with two such retinoids, the all-trans and 13-cis isomers of retinoic acid.

The RFA, "Metabolism and Physiology of Retinoids and Carotenoids in Humans," issued by NCI, sought applications for cooperative agreements to support research on human metabolism and physiological effects of retinoids and carotenoids. Studies of interest include metabolism in the intestinal mucosa, intestinal absorption, regulation of gastrointestinal uptake and tissue concentrations, and extra-intestinal metabolism of these compounds. The studies should span a range of dietary intakes from RDA levels to levels suspected of being toxic. The proposed research requires innovative approaches to determine the dynamics of absorption and metabolism, target tissue levels and specificities of the various vitamin A compounds and how these determinations would elucidate the roles of dietary retinoids and carotenoids in cellular integrity and resistance to tumor promotion.

The PA, "Clinical Investigator Award," issued by NIA, NIAID, NIADDK, NCI, NICHD, NIEHS, and NHLBI, sought applications for clinical investigator awards that would assist promising clinically trained individuals to develop into independent biomedical investigators. It enables candidates to investigate a well-defined problem under a sponsor competent to provide guidance in the chosen area of research. Some of the areas of research emphasized include clinical nutrition and aging, digestive diseases and nutrition, and epidemiology and nutrition.

The RFA, "Perinatal Emphasis Research Center-Intrauterine Growth Retardation," issued by NICHD, solicited applications for a Perinatal Emphasis Research Center (PERC) to focus on intrauterine growth retardation. Investigators are invited to propose studies with a significant clinical component encompassing a wide spectrum of normal and abnormal fetal growth and development, as well as fetal-maternal interactions. Studies may focus on the placenta as it may affect intrauterine growth retardation. For example, studies on the effect of abnormal placental functions on fetal outcome should be considered. Factors affecting the availability of nutrients or substrates



to the fetus offer another area of considerable interest, both in terms of placental function and fetal response to these factors or substrates. New and improved methods for noninvasive monitoring of placental function in patients are needed. Other research areas of importance include studies on the mechanisms by which maternal blood volume is regulated during pregnancy, factors regulating uterine and umbilical blood flow, improved methods for assessing fetal health and development and for early detection of developmental anomalies, and methods for managing intrauterine growth retardation infants so as to maximize infant growth, health and development.

The RFP, "The Analysis of Relationships Between Growth and Dietary Intake Using NHANES Data," issued by NICHD, sought proposals to develop new statistical methodology which can be utilized to analyze the relationships between growth and dietary intake using the NHANES data set. The purpose of the proposed project is to study and develop statistical multiple linear regression models that can be applied to the National Health and Nutrition Examination Surveys I and II data sets in order to analyze relationships between nutrition variables, body measurements, and blood chemistries. These models will take into account the complex survey sample designs of NHANES. Computer software will be developed that will enable researchers to use newly developed regression models in their analyses of NHANES data. The regression models will be applied to the NHANES data to illustrate their applicability and also their utility in providing new information on the complex relationships in these large nutrition data sets.

The RFA, "Core Grants for Clinical Nutrition Research Units," issued by NCI, NIADDK, and NIA, sought applications for core grants in support of Clinical Nutrition Research Units as a means of encouraging the desired multidisciplinary approach to clinical nutrition research. A CNRU is an integrated array of research, educational and service activities that is oriented toward human nutrition in health and disease. The specific objectives of the CNRU solicitation are: 1) to create or strengthen foci in biomedical research institutions for multidisciplinary research in clinical nutrition research in order to develop new knowledge about specific nutrients in health throughout the life cycle and in the prevention and treatment of disease; 2) to strengthen training environments in order to improve the education of medical students, house staff, practicing physicians, and allied health personnel in clinical nutrition; and 3) to enhance patient care and promote good health by focusing attention on clinical nutrition and generating nutrition information for the public. The essential components of a CNRU are: research with human subjects; laboratory investigations; research training; shared facilities and research services; education programs for medical students, house staff, practicing physicians, and allied health professionals; research components of nutritional support services; and public information activities.

The RFA, "The Modification of Eating Behavior and Cancer Prevention," issued by NCI, sought applications for cooperative agreements to support research aimed at developing and implementing methods and



strategies for dietary behavior modification for chronic risk reduction. The specific objectives will be reduction of dietary fat, increase of dietary fiber, a combination of these two, or other dietary modifications associated with a reduction in risk of disease. The behavioral science component of the application should propose methods to measure nutrition knowledge, changes in attitudes, values and other predictors for adoption and maintenance of behavioral changes. The nutrition component should propose valid methods to measure food intake of individual nutrients and particularly fat and fiber and to periodically document the changes in the patterns of fat and fiber intake. Other nutrient intake should also be monitored to assess any possible problems in meeting nutrient needs. There needs to be evidence of adequate expertise in the diet and nutrition area to develop educational materials which might be used in the study such as recipes, shopping lists, exchange lists, and other tools such as shopping guides to facilitate the dietary modification. The study should also consider the use of biological markers for compliance and/or beneficial or harmful effects.

The RFP, "Methodology and Analysis of Vitamin A and Carotenoids in Foods," issued by NCI, sought proposals to support the development of new and improved analytical procedures to measure retinoids and carotenoids in food. Reliable, instrumental methods will be developed for the separation, identification, and quantification of retinoids and carotenoids in foods. Samples for analysis will be selected using sophisticated statistical and marketing information to ensure that representative samples are selected. In order to determine the most significant contributors of retinoids and carotenoids to the U.S. diet, the latest analysis of the NHANES survey will be used to rank foods considering frequency of consumption, portion sizes and their retinoid and carotenoid content. It is estimated that approximately thirty foods account for 85 percent of total vitamin active carotenoids consumed in the U.S. In addition, ethnic foods such as papaya, mango, persimmon, and bitter melon which are important sources of carotenoids for specific population groups shall be included. Most of the retinoids consumed in the U.S. are probably found in less than 10 foods such as liver, milk, eggs and cheeses. Foods should be analyzed as eaten. Regional differences, such as Northeast vs. Southwest, as well as national mean values and measures of the variance of retinoids and carotenoids in foods will also be considered. Individual sampling plans shall be developed for each food. The data will be incorporated into a data base for the calculation of dietary intakes of these compounds in clinical trials, dietary interventions, dietary assessment studies, and nutrition guidance efforts conducted by NCI.

The RFA, "Mutagens in Human Foods," issued by NCI, sought applications for basic studies intended to provide insights and approaches to an understanding of the possible role of food mutagens in human cancer causation and in the possible inhibition of cancer by dietary means. The relevance of dietary mutagens derives from their genotoxic effects which could lead to cancer induction. Concern over dietary mutagens gains further emphasis from the widespread occurrence of mutagens in human foods. Mutagens have been associated with charcoal-broiled steak, boiling of beef stock, broiling of hamburgers at a

relatively modest surface temperature, frying of potatoes and the toasting of bread. Mutagens have also been found to be present in many vegetables, alcoholic beverages, spices, coffee and tea, and various contaminants may also constitute a source of mutagens present in human foods. According to one estimate, the foods and beverages ingested by an individual in the course of a single day might contain 1-2 grams of mutagens. Studies are needed on a small number of mutagens selected from among those which are known to occur naturally in human foods, those found in human feces, and those human dietary mutagens the formation of which is associated with the processing and preparation of food. Compounds of particular interest include, but are not limited to, the following six classes: 1) heteroaromatic amines of the carboline and imidoquinoline types, 2) hydroxylated flavonoids, 3) carbonyl compounds such as acrolein, malonaldehyde and methylglyoxal, 4) fecapentaenes, 5) endogenous N-nitroso compounds, and 6) aromatic hydrocarbons. In addition, analytical procedures need to be developed for the quantitation of the foregoing mutagens in foods, as well as for the quantitation of them and their respective metabolic products present in blood, body fluids, and tissues, and feces. In vitro and in vivo studies relative to the absorption, metabolism and possible carcinogenicity of selected compounds such as quercetin and the human fecapentaenes are also suggested.

The RFA, "The Physiochemical Effects of Dietary Fiber in Humans," issued by NCI, sought applications for cooperative agreements to support research on the physical, chemical, and biologic effects of dietary fibers and their possible protective role in carcinogenesis. Studies of potential interest include the effects of fiber on fecal mutagenic activity, fecal content of bile acids and colon cell kinetics, morphology, and physiology. Investigators are encouraged to be creative and to explore novel physiochemical effects of various fiber fractions. The data supporting the concept of fiber as a protective agent against colon carcinogenesis appear contradictory and somewhat confusing. Part of the problem is that complete information on the nature of dietary fiber is lacking; different dietary fibers produce different physiological responses but isolated fiber components may produce different responses from those of the intact plant. Numerous studies on the physiological consequences of dietary fiber have been undertaken, and multiple mechanisms appear to be involved in producing the wide range of effects associated with enhanced intakes of dietary fiber. A highly controlled and standardized experimental approach is needed to further evaluate the biologic actions of various dietary fibers (both as isolated fiber components and as prototypic foods containing a predominance of one fiber type) and their role, if any, in the protection from carcinogenesis in humans.

The RFA, "Innovative Approaches to Development of Cancer Chemopreventive Agents," issued by NCI, sought applications for basic studies emphasizing innovative approaches to the inhibition and/or suppression of carcinogenesis. Inhibition of the development of cancer by administration of chemical, biochemical, and biological compounds, which directly and/or indirectly inhibit the cancer producing effects of neoplastic and promoting substances is well known in animal systems and may offer an alternate approach to human cancer prevention.

Except for a few types of cancer preventive agents such as the retinoids and certain phenolic antioxidants, most classes of chemopreventive compounds lag far behind in terms of available knowledge concerning the basis of their anticarcinogenic activity. Especially important in the development of innovative approaches to the development of cancer chemopreventive agents will be inquiries into the mechanisms of anticarcinogenesis which take full cognizance of the developing forefronts of molecular biology and carcinogenesis, cellular biology, mechanisms of carcinogenesis and genetic aspects of carcinogenesis such as genetic susceptibility and resistance in experimental animal systems (including known well-defined systems of "spontaneous" tumorigenesis).

The RFA, "Selected Cancer Prevention Clinical Trials," issued by NCI, sought applications for cooperative agreements to support risk reduction clinical trials which are directed toward examining the role of various preventive agents and/or diet in the prevention of cancer. Studies of populations at increased risk to colon, breast, bladder, and head and neck cancer are particularly appropriate at this time. Studies of occupational cohorts who have been exposed to known initiators and/or promoters are also encouraged. Situations where the dose response to the promoter can be estimated are particularly relevant. Recent reports suggest that susceptibility to colon cancer may be related to dietary levels of fiber and/or fat. Dietary fiber and vegetables are thought to be anticarcinogenic, diluting the fecal mass and increasing transit time and possibly contributing to the anticarcinogenic activity. It has been reported that the degradation of certain fractions and/or precursors which are contained in fibers by intestinal bacteria might produce metabolically anticarcinogenic compounds. These might exert protective effects in a number of ways including possible hormonal activity, functioning as weak antioxidants or inhibiting activation of carcinogens by oxidative pathways. A number of animal studies suggest that a high fat diet may promote carcinogenesis in the breast and colon, while epidemiological studies show a positive relationship between dietary fat and breast cancer in some populations. Further clinical studies of fiber and fat balance and their optimization for cancer prevention are indicated.

The PA, "National Research and Demonstration Centers on Ischemic Heart Disease," issued by NHLBI, sought applications from the current Specialized Centers of Research (SCOR's) on ischemic heart disease that detail plans for demonstration and education research activities that are thematically related to ischemic heart disease and for core activities that will serve to coordinate and integrate the various components of the NRDC's. New approaches to disease prevention, health promotion, and improved health care practices are sought. The prevention and control of ischemic heart disease will require a fundamental understanding of its pathogenesis and etiology, effective diagnostic and therapeutic maneuvers, as well as the knowledge needed to improve patient understanding of ischemic heart disease and what can be done to control it. Studies are to consider the modification in patients of identified risk factors such as smoking cessation, antihypertensive therapies, dietary and pharmacologic measures for modifying hypercholesterolemias, weight loss, and/or exercise regimens.



The RFP, "Isotretinoin Basal Cell Carcinoma Prevention Study," issued by NCI, sought proposals for a double-blind randomized clinical trial to evaluate the efficacy of isotretinoin in the prevention of basal cell carcinoma. General requirements of participation include identification and accrual of patients (an average of 12 per month for 18 months), provision of medical screening, determination of patient eligibility and baseline medical evaluations, the storage, dispensing, and accountability of study medication, provision of specified treatments and followup evaluations in compliance with the protocol and administration of the study. Basal cell carcinoma is a tumor of epithelial origin, characterized by uncontrolled multiplication of cells lacking normal maturation and orderly keratinization. Deprivation or deficiency of vitamin A promotes tissue metaplasia and neoplasia in various animal and organ culture models. Retinoids have been shown to delay the appearance, retard the growth, and cause the regression of cancers of the skin, respiratory, urinary, and gastrointestinal tract, pancreas, stomach, cervix, and mammary gland. Several epidemiological studies have shown an association of low dietary intake or serum levels of vitamin A with increased risk of cancer, notably lung cancer and other tumors of epithelial origin. Through the use of dietary surveys or serum samples collected prior to disease development, these studies have shown a higher risk of developing malignancies in subjects consuming less vitamin A rich foods or those having lower serum levels of vitamin A. Although these studies are not without limitations, they suggest a role for vitamin A intake in the prevention of human malignancies.

The RFP, "Evaluation of Chemopreventive Agents by In Vitro Techniques," issued by NCI, sought proposals for contracts to evaluate chemopreventive agents by in vitro techniques. Agents with potential chemopreventive activity are identified by epidemiologic surveys, initial laboratory (experimental) findings, observations in the clinical setting, or structural homology with agents having known chemopreventive activity. The potential chemopreventive agents that can be examined by these techniques run the gamut from all of the retinoid compounds, the antioxidants, growth factor analogues, inhibitors of promotion and antibodies to promoters to synthetic viral polypeptide vaccines. A rigorous and systematic evaluation of these candidate agents is necessary before their efficacy can be examined in clinical trials for cancer prevention. In vitro screening and evaluation techniques measuring the ability of these chemopreventive agents to inhibit transformation provides a relatively rapid and efficient means of qualifying these agents for further evaluation in the prevention of cancer in humans.

The RFP, "Community and Cohort Surveillance Program (CCSP) - Field Center," issued by NHLBI, sought proposals for the establishment of four geographically dispersed field centers, one of which must examine a cohort which is predominantly black and one must also provide services of an ultrasound reading center. A coordinating center and two central laboratories for CCSP are also solicited. The communities studied must be a single contiguous area and have a population of at least 80,000 between the ages of 25-75 years, unless reliable



evidence can be presented that it is a high risk coronary heart disease community. The populations must be stable and willing to cooperate with long-term cohort followup. The cohort must contain approximately 4,000 participating men and women ages 45 to 64 years at entry and individuals with prevalent CHD should not be excluded. The investigator may choose a sampling plan to select a cohort representative of either the age, sex and ethnic composition of the community surveyed as a whole, or the black residents in the whole community. Each contractor is expected to participate as a member of the steering committee and its subcommittees in the development of the protocol, the manual of operations and the specific forms (or computer formats) used for recording interviews, and abstracting exam results. Each contractor will also assume responsibility for pretesting the recruitment methods and data collection materials and procedures. The list of risk factors to be measured, although subject to change during protocol development, are likely to include measures of blood lipids, lipoprotein cholesterol and apolipoproteins, ultrasound measurements, blood pressure and pulse rates, fasting blood glucose and insulin, smoking, alcohol, physical activity, previous body weight, special diets, dietary supplements, dietary calcium, family history of cardiovascular diseases, education, occupation, etc. The cohort will be examined approximately 3 years after the beginning of the trial and will be contacted subsequently annually to ascertain the occurrence of cardiovascular events, medical care received for risk factors or cardiovascular conditions, and address changes. Community surveillance for hospitalized myocardial infarction and CHD deaths will be established as part of the protocol. All cohort and community surveillance data must be sent at frequent intervals to the coordinating center at least every 2 weeks for analysis.

The RFP, "Community and Cohort Surveillance Program (CCSP) - Coordinating Center, issued by NHLBI, sought proposals to establish a coordinating center that shall participate in the planning and conduct of the CCSP. Its responsibilities relate to the cohort component, the community surveillance component, and the interaction between these components, and include certain administrative functions necessary for the planning and conduct of the overall project and the analysis of the data. Data entry for the cohort component will be done at each field center and will use microcomputers that have been programmed by the coordinating center for analysis. In terms of the cohort component, the coordinating center shall provide administrative leadership and scientific coordination for the development of the final protocol, including sample selection, recruitment, examination and follow-up procedures, as well as develop or modify existing database management systems capable. The center shall also provide administrative leadership and scientific coordination for the development of the protocol for the community surveillance procedures.

## **APPENDIX I**

### **FY 1984 SCIENTIFIC SEMINARS**



In FY 1984, ten scientific seminars in nutrition were presented at the monthly NCC meetings by scientists engaged in nutrition research who are supported by the extramural and intramural programs of NIH as well as scientists involved in nutrition research at other government agencies. Descriptions of the seminars follow.

- 1) "Mechanisms of Food-Induced Behavioral Reactions," was presented by John Crayton, M.D., Department of Psychiatry, University of Chicago, at the November 3, 1983 NCC meeting. A summary of his presentation is given below.

The mechanisms by which foods such as chocolate, wheat, and milk might produce behavioral effects such as depression, fatigue, irritability, aggressive behavior, and even psychosis are not yet defined; however, it appears that histamine, prostaglandins, bradykinin, serotonin, arachidonic acid derivatives, etc. may play a role. Studies suggest that individuals with food sensitivities may have an abnormal capacity to clear food-containing immune complexes from the circulation. Other studies have shown elevated levels of immune complexes in food-sensitive subjects. Since immune complex disorders are frequently associated with the mobilization of the serum complement system, it is of interest that various components of complement have been reported to be abnormally low in food-sensitive subjects.

In order to examine the serum levels of complement components and immune complexes in food-sensitive subjects and in a normal asymptomatic control group, both groups were given a series of double-blind placebo-controlled food challenges. The food-sensitive subjects complained most commonly of depression, fatigue, irritability, anxiety, and mental confusion in response to eating certain foods such as wheat, corn, chocolate, eggs, milk, and peanuts. The subjects included 12 normal asymptomatic and 23 symptomatic subjects (4 diagnosed as schizophrenic and 19 having major affective disorders). Each day the subjects received a food challenge with approximately 15 grams of encapsulated powdered food or placebo. Each morning a series of baseline behavioral measurements were made and blood was drawn for immunological studies. The behavioral measurements were repeated at 1, 4 and 8 hours after the food capsules were administered, while the immune measures were made at 4 hours. Complement assays for total hemolytic complement (CH50), complement immun adherence (CI), C1Q, C3, C4, C5, and C3A were performed. Inspection of the data revealed that symptomatic subjects have lower levels of C1Q and C4 when compared with asymptomatic subjects. Levels of C3A show a greater range of values with more low and high values, compared with asymptomatic subjects. There were more elevations of immune complex levels as measured by Raji cell assays in the symptomatic subjects compared to the asymptomatic group.

To determine whether there was a relationship between the ingestion of food (or a particular food) and complement or immune complex levels, the effects of milk, wheat and chocolate were studied in the symptomatic group, while wheat and milk were studied in the asymptomatic



matic group. This analysis yielded a similar pattern in both the asymptomatic and symptomatic subjects. Part of the difficulty in deciphering the effects of particular foods on complement and immune complexes is that there is considerable interindividual variability in the pattern of response of complement and immune complexes. It appeared that patients complaining of depression, fatigue, and other psychological dysfunction in response to foods have significantly lower levels of several components of complement and significantly higher levels of immune complexes when compared to asymptomatic subjects. The relationship between these findings and the actual ingestion of food is not clear; no consistent relationship between food ingestion and levels of complement and immune complexes could be found. In symptomatic subjects, the two variables with a significant interaction between test period times and capsule ingestion, Raji Cell (wheat versus placebo) and ClQ (chocolate versus placebo), there was a drop in the measures after challenge with placebo and either no change or a small rise for the active food. Such results may indicate that some abnormality of complement or immune complex formation is related to the patient's symptoms. A number of byproducts of immune complex formation are potentially psychoactive; these include anaphylatoxins, histamine, and serotonin. The exact relationship between these immunological findings and the psychological dysfunction remains to be elucidated.

Another component of this study examined behavioral reactions to three foods: wheat, milk, or chocolate. The foods tested in each individual were selected on the basis of their own food history: 21 received wheat, 12 chocolate, and 8 milk. Subjects were given one food or placebo challenge per day during the 8-day test period. Each morning and again at 1, 4, and 8 hours after capsule ingestion, subjects completed the Profile of Mood States (POMS), the Addiction Research Center Inventory, a visual analogue scale of eight descriptors of behavior, and a group of neurological tasks including a Continuous Performance Test, a Reaction Time Test, a Digit Recall Test, and a test of finger tapping speed. These behavioral measures were carried out in addition to the battery of immunological measures previously described. The effects of food, placebo, and time after presentation of capsules were examined using analysis of variance. Separate analyses were conducted for trials of wheat, milk, and chocolate versus placebo for both groups, since examination of the data suggested that the effects of different foods on mood status would likely differ in both direction and magnitude from one another.

Analyses of the data revealed significant differences between the POMS ratings for the symptomatic and asymptomatic groups assessed at the 32 time periods during the study. Symptomatic subjects showed higher scores for anxiety, depression, fatigue, and confusion and lower scores for vigor, friendliness, elation, arousal, and positive mood. There does not appear to be any clear pattern to the variation between the two groups on 6 of the 10 POMS subscales with statistically significant differences. Inspection of individual responses showed that the food challenges may have had a significant effect in some symptomatic individuals, e.g., wheat and chocolate challenges appeared to precipitate large changes in POMS scores on days 6 and 8;

chocolate in particular caused an increase in POMS anxiety and anger subscales while wheat and milk produced large changes in positive mood. Few such behavioral relationships could be found in the asymptomatic group.

In order to determine whether specific foods such as wheat, chocolate, and milk were likely to produce behavioral reactions, a series of ANOVA's were done. Significant interactions were found for the interaction wheat and test period in the symptomatic groups for four of the 10 POMS subscales: vigor, confusion, arousal, and positive mood. The interaction between milk and test period appeared significant on the positive mood scale, whereas it approached significance for depression and elation. No significant interactions were found for chocolate and test period.

The results of the study indicate that the symptomatic subjects had higher negative mood states and lower positive mood states than asymptomatic subjects in response to food challenges. The symptomatic group showed many more significant differences when food was compared to placebo challenges than did the asymptomatic group. In terms of the three foods tested, wheat produced higher positive mood states and lower negative mood states at 4 hours compared to both placebo trials at 4 hours and compared to the wheat trials at baseline for all of the subscales with significant interactions between food and test period.

The mechanisms for the effects of food on behavior remain unknown. It is possible that the POMS subscales are not able to accurately reflect change in the direction for the symptomatic subjects in this setting, and therefore the ways in which this instrument interacts with both the testing environment and the subjective phenomena of individual's reactions to foods needs to be investigated. The solution to this problem will come only when a pathophysiological mechanism or mechanisms are identified that mediate behavioral reactions to foods. Then the steps in the pathophysiological pathway can be monitored and correlations between behavioral reactivity and these biological mechanisms demonstrated. Results of immunological studies suggestive of complement activation and immune complex formation in these patients suggest presence of biological "markers" of reactivity. Thus, the data generally support the concept that some peculiarly sensitive individuals respond to certain foods with disruptions in behavioral functioning. In view of the many sources of potential error, this conclusion must be considered tentative.

Dr. Crayton concluded with a description of another study involving patients who complained of major psychopathological and cognitive reactions to foods. In this group, several complement proteins were abnormally low as compared to an asymptomatic control population. Whether these changes in complement were related to some specific immunological event provoked by food ingestion or whether they represent a less specific alteration in immune function is not yet known. These changes suggest, however, that individuals with psychological and cognitive dysfunction may harbor a biologic defect which predisposes them to or which mediates food intolerances.

Among the methodological procedures needed to adequately demonstrate the putative phenomenon are: adequacy of blind food challenges, control of dosage factors, use of reliable and validated measures of behavioral change, adequate characterization of the susceptible population, and application of acceptable research design and statistical analyses techniques.

- 2) "Animal Models for Human Nutrition Research," was presented by Carl Hansen, Ph.D., Geneticist, Veterinarian Resources Branch, Division of Research Services (DRS), at the December 1, 1983 NCC meeting. A summary of his presentation is given below.

The NIH Animal Genetics Resource Program (AGRP) of DRS is designed to support biomedical research by maintaining colonies of genetically defined small research animals and developing new strains. While it is recognized that clinical studies with humans are the most appropriate means of conducting medical research, there are many areas in which animal studies are critical for understanding basic life processes and delineating cause and effect relationships. Much of what has been learned about basic life processes has been gained from animal studies and the importance of the role of genetics in these processes, as well as in disease processes, was established by genetic studies with animals.

The AGRP evolved from a program established some 30 years ago to produce genetically defined research animals for the NIH intramural program. Since that time, the program has become one of the major resources of genetically defined small research animals. Currently, the resource consists of more than 250 closed breeding groups including inbred strains, congenic strains, and outbred and mutant stocks of the more commonly used small research animals. Many of these strains were acquired from other investigators; however, a substantial number have been developed from internal resources. In more recent years, the AGRP has been active in establishing and maintaining genetically unique stocks which were in danger of becoming extinct. To assist in this endeavor, an embryo cryopreservation program has been established. Due to its impact beyond the NIH intramural program, the AGRP has been designated by the World Health Organization as a resource center for laboratory animals, as well as an international center for nude mice.

The research animals which make up the AGRP reflect the broad spectrum of research under way in the NIH intramural program. The program can be divided into two broad categories of research animals: those strains which were established elsewhere and introduced into the AGRP at the request of the NIH research community, and those strains which were developed internally. As a result, a variety of animal models are available for studies of basic immunology, oncology, metabolic diseases, hypertension, behavior, disorders of the nervous system, alcoholism, and resistance or susceptibility to pathogens.

Dr. Hansen concluded that the rationale for undertaking development of a particular strain of animal stems from either a request from an



investigator, or the recognition by DRS personnel that a particular animal model system may be useful to a certain segment of the research community. At the present time, no projects are under way specifically designed for nutrition research. However, the results obtained from one project suggest some interesting interactions between obesity, diabetes mellitus, hypertension, and brown fat activity since it appears that an expression of a particular gene is modified by the genetic background of the animal. This finding may illuminate the relationship of obesity and insulin independent diabetes mellitus.

- 3) "The Effect of Exercise on Food Intake," was presented by Xavier Pi-Sunyer, M.D., Associate Professor of Medicine, Columbia University and Chief of Endocrinology, St. Luke's-Roosevelt Hospital, at the January 5, 1984 NCC meeting. A summary of his presentation is given below.

Studies on energy balance consider both sides of the balance equation, i.e., energy intake and energy expenditure. While physical activity undoubtedly adds to the expenditure side of the equation, its effect on intake remains unclear. Early studies in animals have reported compensatory increases in intake with moderate levels of exercise but paradoxical decreases with mild levels. This work also suggested the existence of a zone of physical inactivity where energy intake fails to decrease in response to decreased expenditures. Overweight and obesity are the likely result. The excess body fat of sedentary obese subjects, therefore, may be partly the result of a breakdown in activity related regulation of intake.

In humans, support for such a phenomenon is only obtainable through systematic, metabolic balance studies. One study on the effect of increased physical activity on energy intake and balance was conducted in six obese women (mean weight: 167 percent above ideal body weight) who underwent three 19-day periods--one sedentary and two with treadmill exercises which increased daily expenditure to 110 percent (mild) and 125 percent (moderate) of sedentary expenditure. Regardless of the exercise added or subtracted from daily activity, the energy intake of these women remained fixed at the level equal to sedentary expenditure. A significant negative energy balance was obtained when exercise was added to the regimen because no compensatory increase in energy intake occurred with increased energy expenditure. Results indicate that individuals chose their given energy intake level during the first treatment period regardless of which exercise regimen was assigned. Energy intake remained independent of expenditure throughout the study. Therefore, these results suggest that in obese women, exercise at moderate, realistic levels does not regulate intake, at least within 19-day periods. Since no hyperphagic response occurred, negative balance during exercise treatment was obtained and produced a significantly greater rate in fat loss.

In order to study if this effect would be sustained over a longer period of time, a second group of obese female volunteers was maintained for three 19-day periods at 125 percent of their sedentary expenditures. In this study, food intake, energy balance, and body



composition were recorded. Individual sedentary expenditures ranged from 2,026 to 2,575 kilocalories/day (mean: 2,276 kilocalories). During the three 19-day periods of moderate exercise the period means for expenditure were constant with a mean of  $2,882 \pm$  kilocalories/day or 127 percent of sedentary values. Since energy intake for the subjects ranged from 1,777 to 2,140 kilocalories/day, energy balances were highly negative and did not change between periods. The intake levels selected by the subjects were proportional to their daily expenditure level so that the resultant energy balances were not different among subjects. In terms of body composition, mean total body weight and fat content decreased significantly with treatment whereas lean body mass did not change. Fat changes comprised 89.3 percent of the total tissue lost in these subjects.

Results from this study support the conclusion that exercise at moderate, realistic levels in obese women does not regulate energy intake. Since the subjects did not change their intake during the 57 days of exercise, the effect persists over time. Also the high proportion of fat lost by these subjects may reflect the effect of an exercise-induced preferential fat loss in very obese persons who possess a greater percentage of fat in their adipose tissue, as well as a lean body mass accumulation secondary to exercise. These subjects also experienced a decrease in basal metabolic rates which may be attributed to the greater caloric deficit incurred (about 1,000 kilocalories/day), the significant weight loss obtained, or a combination of the two. Moderate exercise in these obese women did not prevent the fall in resting metabolic rate. The effect of these decreases in metabolic rate on total daily energy expenditure was not significant due in part to the wide range of variation in other activities. For example, the metabolic cost at a given rate of walking decreased, due to adaptation to the exercise and/or a decrease in energy expenditure with weight loss. The study revealed that exercise must be progressively increased in a long-term treatment in order to sustain a consistent rate of weight loss.

Dr. Pi-Sunyer concluded that although an increase in physical activity did not decrease intake, a compensatory intake response also was not produced. The combination of moderate exercise with energy intake at the level self-selected in this study produced a negative energy balance. Therefore, exercise can be a useful treatment for weight reduction if combined with a palatable but not gourmet diet.

- 4) "Parental Factors in Childhood Weight Control," was presented by Leonard Epstein, Ph.D., Associate Professor of Psychiatry, Epidemiology and Psychology, Western Psychiatric Institute and Clinic, University of Pittsburgh, at the February 2, 1984 NCC meeting. A summary of his presentation is given below.

Childhood obesity is an important research problem for a number of reasons: obese children are likely to become obese adults; excess weight in children is reliably related to elevated blood pressure; and behavior problems may be related to excess weight, e.g., depression, the personality factor that correlates most highly with relative weight.

It is known that one of the major contributing factors to childhood obesity is the weight of the parents and that children with two obese parents have two to three times the amount of fat as children with two lean parents. Furthermore, children with heavy parents are more likely to become obese than are children with lean parents. Clinical family-based research has also shown that parents and children lose weight at very similar rates.

The present study attempted to define the role of parental weight in childhood weight loss and related physiological and behavioral components of obesity--blood pressure and social withdrawal. In addition, the concept of parental versus child self-control in eating behaviors was examined. For the study, 36 obese children were stratified into either the thin-parents group (17 children) or the heavy-parent group (19 children with at least one obese parent) and then randomized into parent control (PC) or child self-control (SC) groups forming a 2x2 factorial design in which heavy or thin parents were crossed with parent or child self-control. Both the children and the overweight parents were provided a 1,200 calorie diet along with a lifestyle exercise program and were seen separately by the counselors. Parents also deposited \$85 for a contract, the deposit to be returned upon satisfactory attendance at treatment and maintenance meetings.

The children earned points for exercising, eating properly, and losing weight. In the parent control group, the parents awarded the points; in the child self-control group, the children awarded themselves points. Parameters measured in the study included height, weight, body composition and blood pressure of both children and parents, nutrient analysis, eating behaviors, and fitness and behavior profiles of the children.

Results showed significant differences in total weight loss, body mass index (BMI), and percent overweight between the thin and obese parent groups with obese parents showing the most change. At 12 months, obese parents had lost 15.2 pounds, 2.6 BMI units and 10.9 percent body weight while thin parents had lost 6.8 pounds, 1.1 BMI units and 5 percent body weight. For the children, weight changes during the first 6 months of treatment were generally similar for those with thin or heavy parents. However, while all children tended to gain weight between 6-12 months of treatment, significant differences were observed in the rate of growth in children with thin parents as compared to children with heavy parents. At the end of one year, children with thin parents were 5 pounds lighter, while children with one heavy parent were 1.2 pounds heavier and those with two heavy parents were 5.7 pounds heavier. BMI units and percent overweight changes relevant to the number of heavy parents were not significant. In terms of fitness, children with heavy parents generally had higher heart rates and thus were less fit than children with thin parents. At 6 months, exercise and recovery heart rates had all significantly decreased, but children of heavy parents still had higher heart rates during exercise than children with thin parents. In terms of behavior, significant improvements in school competence and decreases in aggression and social withdrawal were observed after weight loss. However, these changes were not related

to weight change, and were not analyzed further. Given that obese parents may be withdrawn, parental behavior must be considered as likely a causal agent for childhood depression as childhood overweight.

It is interesting to note that while heavy parents lost more weight than thin parents, children with thin parents lost more than children with heavy parents. The child weight changes clearly show the importance of parent weight on child weight change. Significant decreases in body fat, girth, and systolic and diastolic blood pressure with treatment were observed in both obese children and parents regardless of parental weight. The differences in fitness as a function of parental weight may be due to two sets of variables: 1) Thin parents may support more activity than heavy parents, thereby producing more fitness; and 2) the hereditary component of fitness by which genetic differences in parental fitness may determine their activity level which would directly affect their weight. The data also suggest that child blood pressure levels and change are likely to be a function of parental blood pressure levels and not parental weight categories. The study revealed no differences in effects between programs in which the parents were in control of the motivating reinforcing agents versus one in which the child was in control.

Dr. Epstein concluded that this study provided information on the role of heavy parents in determining the effect of treatment for their children, and on the interaction of child and parent weight in determining physiological and behavioral risk factors for obese children. The study clearly points out that weight loss in children is affected by parental weight. Other factors which can affect weight change include genetic makeup, developmental differences in energy balance, and behavioral factors. The interrelationship between the physiological, behavioral, and cognitive variables needs to be examined further in order to understand the etiology and consequences of obesity and related risk factors.

- 5) "Human Nutrition Research and Information Management (HNRIM) System" was presented by Artemis P. Simopoulos, M.D., Chairman, NCC; John Myers, Director, Current Research Information System (CRIS); USDA, Thomas P. Vogl, Ph.D., Expert, NCC; and Judy Mahaffey, Senior Systems Analyst, Division of Computer Research and Technology (DCRT), NIH, at the March 1, 1984 NCC meeting. A summary of their presentation is given below.

Dr. Simopoulos presented the history of the development of the "Human Nutrition Research and Information Management (HNRIM) System," from the original data retrieval system for nutrition research developed by the NIH in 1977. At that time, human nutrition research and training was defined by the NCC, and the data retrieval system developed was based on that definition. In 1980, the Joint Subcommittee on Human Nutrition Research of the Office of Science and Technology Policy, Executive Office of the President, utilized an expansion of the NIH system to include all Federal agencies supporting human nutrition research (at present, Department of Health and Human Services, U.S. Department of Agriculture, Veterans Administration,



Agency for International Development, Department of Defense, National Science Foundation, National Oceanic and Atmospheric Administration, and National Aeronautics and Space Administration). The JSHNR effort involved the development of a Federal definition of human nutrition research suitable for data retrieval, based on an expansion of the NIH definition, and the subsequent development of a data classification system for nutrition research. Subsequently, Congress amended Section 1427 of the National Agricultural Research, Extension, and Teaching Policy Act of 1977 by the National Agricultural, Research, Extension, and Teaching Policy Act Amendments of 1981 and mandated establishment of the HNRIM system, as noted on page 89 of this report. In response to this mandate, the Secretaries of Health and Human Services and USDA asked the JSHNR to develop the Human Nutrition Research and Information Management System. The joint USDA-DHHS Task Force on HNRIM was then established to develop the system and was cochaired by representatives of USDA and DHHS.

Dr. Vogl, the DHHS cochairperson of the task force and the HNRIM system coordinator presented the work of the task force in establishing the system. The task force first reviewed the classification system and the list of data elements previously developed by the JSHNR for data retrieval, and made slight editorial modifications in the classification system. The task force then developed more detailed specifications for the computer data system that is in the final stages of being implemented by the Division of Computer Research and Technology under the leadership of Judy Mahaffey.

Mr. Myers, director of the USDA Current Research Information System (CRIS), discussed his agency's perception of the HNRIM system, and the need for making the data base available through a commercial data base vendor for use by researchers at the land grant colleges and USDA staff throughout the country. He described USDA's role in making the data base available through the DIALOG data system which also houses USDA's CRIS, the USDA analog of the NIH CRISP system.

A technical description of the system was provided by Ms. Mahaffey who explained the system's capability to search the various data items, including the narrative portion for either words or groups of characters. Access to the system is available through remote terminals connected to the computer by telephone lines. The computer program assists the user by asking question via the terminal. As an example, a search for research projects that address the interaction of iron and vitamin C was shown. The strategy consists of searching the narrative of all projects that are identified by classification code 21, vitamins, and classification code 22, minerals and essential trace elements, for the characters ("iron" or "Fe") and ("vitamin C" or "ascorb"). Ms. Mahaffey announced that tutorials on the use of the system will be held for Federal employees in the fall of 1984.

6) "NEI-India Collaborative Research on Prevention of Blindness," was presented by Barbara Underwood, Ph.D., the NEI representative to the NCC and P.G. Tupule, Ph.D., former Director, National Institute of Nutrition, India, at the May 10, 1984 NCC meeting. A summary of their presentation is given below.



There are an estimated 40 million blind people in the world and 60 to 80 percent of this blindness is preventable or curable. Because the major causes of blindness--cataract, glaucoma, and senile macular degeneration--are age-related in the developed world, by the year 2000 there will be a twofold increase in the total number of blind people unless preventive steps are taken immediately. Viewed globally, about 70 percent of the blindness can be attributed to four causes: 1) cataracts; 2) trachoma; 3) onchocerciasis; and, 4) xerophthalmia. Xerophthalmia, the term used to describe several reversible clinical symptoms associated with visual impairment due to vitamin A deficiency, is estimated to afflict 5 million people annually in Asia alone, primarily children. Keratomalacia, the partial or totally irreversible blinding form of xerophthalmia, is estimated to affect 250,000 children annually in Asia. Its primary cause is also vitamin A deficiency, however it is complicated in most cases by severe protein-calorie malnutrition.

From its inception, the NEI has been concerned about blindness prevention around the world, and this problem has been addressed as part of the Institute's research program. Research activity in the prevention of visual impairment from vitamin A deficiency was considerably enhanced in 1976 as the result of a workshop on keratomalacia held at the NIH. The workshop participants identified several areas of needed research in the field, and established the consensus on the need for a clinical research center located in an area where the problem is endemic, and associated with an established clinical or research facility.

In 1980, the National Institute of Nutrition (NIN) at Hyderabad, India was selected as the site for this clinical research facility. The NIN has a long and distinguished history in nutrition research which began in 1918 under the direction of Robert McGarrison in a one-room laboratory at the Pasteur Institute at Coonoor. The programs that have evolved through the years under the leadership of a series of well-known nutrition scientists have made it one of the outstanding institutes for nutrition research and training now in existence in Asia. NIN has a history of research in vitamin A deficiency and was the institution selected to pilot test a program using a semiannual prophylactic massive oral dose of vitamin A (200,000 IU). The NIN is a self-contained, well-equipped research facility with access to patient populations in local hospitals, including a children's hospital and an eye hospital. It occupies 33 acres of land, has a professional staff of over 150 persons and adequate housing facilities including an international hostel to accommodate visiting scientists and students.

In 1980 and 1981, scientists from the NEI and NIN worked collaboratively to develop a research program that addressed issues surrounding the xerophthalmia/keratomalacia problem and was relevant to the planning and implementing of prevention programs. Six study protocols underwent peer review and approval procedures, both at NIH and in India. The six protocols include: 1) the study of the relationship of measles and vitamin A status to the development of related keratomalacia and blindness in children; 2) the evaluation of methods

for identifying subclinical vitamin A deficiency; 3) the analysis of the role of anterior segment collagenase activity in the development of keratomalacia; 4) comparison of vitamin A absorption in diarrhea treated with and without oral rehydration solution; 5) a case-control study to determine risk-factors in the development of keratomalacia; and, 6) studies on the relationship of vitamin A status to immunocompetence and infectious morbidity. The bilateral exchange of scientists is a part of this program. Until late in 1982, administrative matters delayed the actual implementation of the scientific protocols. Two of the study protocols implemented in late 1982 are due for completion by the end of 1984, and two additional protocols will be implemented by fall 1984. The remaining two protocols are likely to be implemented in 1985. Results to date have provided useful and relevant information for use in programs to prevent nutrition blindness in India.

As a result of the visit of President Indira Gandhi with President Reagan in 1982, a new Science and Technology Initiative (S&TI) in collaborative research developed. This initiative, which originally had a 2-year timeframe, includes studies in health as well as in agriculture and photovoltaics. The National Science Foundation, which was assigned to provide support for the program, transferred the money to support the health initiatives through the Fogarty International Center to three Institutes: NIAID, NICHD, and NEI. The research programs of these Institutes were identified by a high-level panel of senior scientists as being of high priority in the approved areas of blindness prevention, immunology, and reproductive physiology. The programs are to be conducted in collaboration with the Indian Council of Medical Research. This new S&TI permitted NEI to expand its collaborative program with India. Expansion of the program includes a hospital-based, case-control study to be implemented by the Fall 1984 and carried out in collaboration with the Rajendra Prasad Eye Hospital in New Dehli. This study will investigate the risk factors of senile cataracts with emphasis on nutritional and biochemical as well as environmental parameters. The laboratory analysis for trace elements will be done at the Institute of Occupational Health in Ahmedabad, India.

A second study under the S&TI agreement being conducted in collaboration among NEI scientists and consultants, and the Aravind Eye Hospital and the Kamaraj Madurai University scientists in Madurai will consider Eales' Disease, a disease-related blindness problem in India. Eales' Disease is a blinding disease affecting primarily males between 20-30 years. The etiology is unknown, but in many respects the symptoms resemble those seen in diabetic retinopathy. The study, which is in the early stages of implementation, will look at the natural history of the disease, its treatment, and the immune status of those affected.

Under the S&TI agreement, the studies at NIN on collagenase and the absorption from oral rehydration solution will also be facilitated. In addition, technology transfer in the use of monoclonal antibodies in NIN research will be accomplished through the training of staff. This training will explore the use of this technique for identifying early signs of vitamin A deficiency.

- 7) "The Psychology and Physiology of Obesity," was presented by Kelly Brownell, Ph.D., Visiting Scientist, Health Promotion Sciences Branch, NCI, at the June 7, 1984 NCC meeting. A summary of his presentation is given below.

Obesity is one of the most difficult medical and psychological problems of modern society. Studies have shown obesity to be associated with hypertension, hyperlipidemia, diabetes mellitus, surgical risk, pulmonary and renal problems, and complications during pregnancy. Results from a number of epidemiological studies have shown that weights above desirable weight are associated with increased mortality and that obesity is an independent risk factor for cardiovascular disease. In addition to the medical hazards of obesity, obese individuals also suffer psychologically and socially since society has a strong bias against overweight persons. Obese people not only suffer from the stigma of their obesity but also from being blamed for their condition. In addition, some of the psychological problems of obesity lie in its treatment, since dieting is associated with a number of emotional symptoms.

The set point theory of body weight regulation is based on the observations that a great variability in weight exists among individuals, although the weight of most individuals remains remarkably constant over time. Studies in animals as well as in humans suggest strong resistance to changes in weight; e.g., animals have been shown to adjust food intake and physical activity to compensate for starvation or forced feeding. The same regulation may occur in humans.

Physiologically, weight gain can occur through an increase in the number of fat cells (hyperplasia) or by enlargement of existing cells (hypertrophy). One popular theory pertaining to fat cells has been that weight loss and gain during adult years could occur only by increases and decreases in cell size. However, new evidence suggests that hyperplasia can occur in adulthood, i.e., cell number can be increased but not decreased. This implies that weight gain may irreversibly increase fat cell number. One study of weight reduction in both hyperplastic and hypertrophic women revealed that weight loss ceased when fat cell size reached normal, even though they stopped losing weight after varying lengths of treatment and widely varying weight losses. Fat cell size, therefore, may set the biological limit to weight loss, whereas fat cell number may determine the weight at which this limit occurs. The American diet may also lead to weight gain, and obese persons may be cursed by a biology that prefers "fattening" foods. Studies have shown that, collectively, sweetness, fat content, and variety form a combination almost certain to create obesity, at least in laboratory animals. Such a diet may influence body weight by increasing adipose cellularity which may then prevent weight loss.

The clinical assessment of obesity is very important and should be a multifaceted plan including the following: a) defining and measuring obesity; b) assessing genetic and biological determinants; c) evaluating eating behavior; d) evaluating physical activity; e) assessing independent variables; and f) assessing the effects of treatment.



The most thorough means of measuring weight reduction is to combine measures of body weight (percentage overweight, absolute weight, and body mass index) with measures of body fat (skinfold calipers).

Since obese people seek treatment for psychological, social, cosmetic, and medical reasons, assessment must take into account these reasons. Measures of self-esteem, marital adjustments, social interactions, job status, body image, psychological adjustment and, if possible, physiological measures of heart rate, blood pressure, etc., should be included in the assessment. Assessment of treatment adherence is also an important issue since determining why a treatment is effective can be as important as determining whether it is effective. Investigations on adherence have considered whether there is an obese eating style and whether changes in eating style lead to weight loss.

Obesity in children is a serious problem not only because of its association with hyperinsulinemia, hypertension, hyperlipidemia, and decreased growth hormone but also because most obese children become obese adolescents and most obese adolescents become obese adults. The psychological and social consequences of obesity in children can also be quite harmful. Some promising clinical approaches for treating childhood obesity include behavior modification techniques that involve the parents and programs through schools. Behavioral modification programs that include family involvement, exercise, nutrition education, and traditional behavioral techniques have shown favorable weight losses and encouraging reports of maintenance. Parents exert a powerful influence on the eating and physical activity patterns of their children. Studies have shown that a child with two obese parents has three to eight times the chance of being obese than a child with two lean parents. In terms of the exact role of parents in the treatment of their obese children, more research is needed to better understand the relationship between parents and their children.

Studies on treating obesity in schools have shown that significant weight losses were obtained with programs combining nutrition, exercise, behavior modification, and psychological support. For example, one study of 5- to 12-year-old school children revealed that during the 10-week program 95 percent of the children lost weight compared to 21 percent of controls. Children in the program lost 9.7 pounds and decreased their percentage overweight by 15.7 percent.

Four major contributions of behavioral programs for obese adults are: 1) a sensible group of procedures and principles has been developed to teach patients changes in eating habits; 2) attrition is reduced; 3) untoward emotional symptoms that occur with some other approaches do not occur with behavior therapy; and 4) methods for studying weight and behavior change have been greatly improved.

Physical activity is critical in determining whether a person loses weight and whether the weight loss is maintained. Obese adults appear to be less active than nonobese adults, but the same does not hold true for obese and nonobese children. It may follow that inactivity is a consequence rather than a cause of obesity and that



inactivity may maintain obesity even if it did not contribute to its development. The five reasons why exercise is important for weight reduction are that exercise may: (a) increase energy expenditure, (b) counteract ill effects of obesity, i.e., have a positive influence on plasma insulin levels, lipid levels, blood pressure, etc., (c) suppress appetite, (d) increase basal metabolic rate, and (e) minimize loss of lean tissue. Studies have shown that routine exercises like walking and using the stairs may hold the greatest promise for the obese person. Attrition is a serious problem with approximately 50 percent of participants dropping out. Studies have shown that reinforcement, contracting, and social factors seem to be useful in maintaining participation.

Dr. Brownell concluded that innovative research approaches on the physiological, psychological and social factors related to the genesis and treatment of obesity are needed. Research on children and adults is needed, as well as studies on the issue of short-term versus long-term weight loss maintenance. Dr. Brownell explained that one approach he is investigating is the application of worksite weight loss competitions. Such competitions have worked well in both business and industrial settings with groups that range in size from 150 to 1,200 persons. Participants are assigned to teams and are given a weight loss goal based on their desirable weight. The team that loses the greatest percentage of their weight loss goal over a 12 week period is awarded the prize money. The dropout rate for such competitions is less than 1 percent and the mean weight loss is approximately 5.5 kilograms. The program was favorably rated by both management and employees. The competitions have a favorable cost-effectiveness ratio when compared to other programs. Such results raise interesting questions about the relative importance of education and motivation since positive results are produced with a less intensive program, presumably because of the increased motivation and social support.

- 8) "Dietary Protein and the Incidence of Cerebral Lesions in Stroke-Prone Rats," was presented by Walter Lovenberg, Ph.D., Chief, Section on Biochemical Pharmacology, NHLBI, at the July 12, 1984 NCC meeting. A summary of his presentation is given below.

Studies on the role of nutrition in the development of cardiovascular diseases have investigated the relationship of sodium intake and hypertension, and dietary lipids and atherosclerosis, coronary artery disease, etc. Preliminary evidence now exists that indicates that the amount or type of protein in the diet may influence the severity of hypertension and its sequelae.

Recently, the effects of dietary factors on the incidence of cerebral lesions in stroke-prone, spontaneously hypertensive rats (SHR-SP) have been under investigation. This strain of rats, derived from the spontaneously hypertensive rats (SHR), has a very high blood pressure (arterial blood pressure >200 mm Hg by 6 months of age) and exhibits an 80 to 90 percent incidence of cerebral lesions during the first year of life. Studies carried out in Japan using this particular strain of rats fed a Japanese commercial rat feed revealed a higher

incidence of cerebral lesions than similar studies carried out at the NIH. The mean blood pressures observed in both the Japanese SHR-SP and NIH SHR-SP were similar; however, the frequency of stroke appeared to be significantly less in the latter group. Such observations suggested that perhaps environmental factors such as diet interacted with the genetic traits for hypertension to account for the high incidence of stroke in the SHR-SP rats. Extensive investigations were carried out to compare the effects of the Japanese rat diet and the NIH open formula diet on blood pressure, incidence of cerebral lesion, body weight, neurological symptoms, etc., in groups of rats fed the different diets. Results of the study revealed marked significant differences in the incidence of cerebral lesions, which was higher in the group fed the Japanese diets. No apparent differences were noted in the type or location of the pathology, although significantly more animals fed the Japanese diet had severe neurological symptoms. Analysis of the nutrient composition of the two diets revealed a higher protein content of the NIH diet and a slightly greater content of free amino acids. Crude protein content and total dietary amino acids were 1.3 to 1.4 times greater. In terms of essential amino acids, methionine content was higher by a factor 1.7 in the NIH diet. Various other differences in vitamins and minerals were not significant.

Clearly, hypertension is identified as one of the major risk factors in the incidence of stroke. In Wistar-Kyoto animals with a normal range of blood pressure below 150 mm Hg, cerebral lesions are seldom seen. In stroke-resistant SHR rats with blood pressures generally below 200 mm Hg, the stroke incidence is less than 10 percent by 1 year of age. This evidence suggests that increased blood pressure in the SHR-SP may be the primary pathogenic factor for stroke in these animals. However, although the animals on the American diet had a decreased incidence of stroke, their blood pressure was not lower than those animals fed the Japanese diet. Blood pressures of all the animals exceeded 200 mm Hg, and there appeared to be no correlation between severity of hypertension beyond 200 mm Hg and subsequent stroke.

Investigators have now found that supplementation with protein was effective in reducing the incidence of stroke. In some studies, the inclusion of 1.5 percent methionine in drinking water significantly reduced the incidence of stroke. Long-term treatment of SHR-SP with taurine, a methionine metabolite, also slightly reduced blood pressure and reduced the incidence of stroke to 30 percent of the control. It is possible that methionine (or derivatives of sulfur amino acids) from the American diet are effective in preventing stroke, even though the amount of methionine in the American diet is insufficient to attenuate severe hypertension. The biochemical basis for the protective effect of added protein on cerebral lesions resulting from severe hypertension is not yet clear. However, the following three hypotheses are under investigation: 1) the sympathetic nervous system has a role in regulating protein synthesis in small vessels which may be modulated by the availability of amino acids; 2) amino acids and amino acid metabolites may serve as neurohormonal agents; and 3) dietary protein may enhance natriuresis.

Studies have shown that one of the early events in the development of hypertension in the rat is an increase in sympathetic nerve activity. One study found that the apparent twofold increase in the rate of amino acid incorporation into vascular noncollagen protein could be normalized by interruption of sympathetic nerve traffic to the vessels. Since either splanchnicotomy or ganglionic blockade resulted in significant decreases in blood pressures, it appeared important to determine whether this physiologic change was responsible for the normalization of amino acid incorporation. Data available thus far confirm that the enhanced amino acid incorporation in vascular proteins of hypertensive rats is due to a trophic effect of the sympathetic nerves, rather than a consequence of hypertension. The apparent increased sympathetic nerve activity often associated with hypertension may also serve a protective role by permitting the hypertrophy and strengthening of the blood vessels. Since most neurohumoral or neurotransmitter substances are nitrogenous compounds derived either directly or indirectly from dietary protein, it is quite possible that dietary protein influences their biosynthesis and utilization. The amino acids tyrosine and tryptophan are precursors for catecholamines and serotonin, respectively, both important neurotransmitters for the central and peripheral regulation of blood pressure. It is quite possible that tyrosine may slightly decrease blood pressure as well as enhance the release of norepinephrine at the small resistant vessels and promote the trophic effect of sympathetic nerves at the blood vessel. Dietary tyrosine might, therefore, serve to both strengthen the vessel and reduce blood pressure, in part accounting for the protective effect of dietary protein on the incidence of cerebral lesions. More research is needed to clarify the role of these transmitters on the protective effect of dietary protein.

The effect of increased protein intake on sodium excretion appears to be important. Both urine volume and sodium excretion in normotensive and hypertensive rats rise with increases in dietary protein. The mechanism of the effect of protein on natriuresis is not known--it is possible that it could be a direct renal effect of the amino acids or their metabolites, or that increases in catecholamine biosynthesis results in neuronally regulated natriuresis.

Dr. Lovenberg concluded with a preliminary epidemiologic study carried out in Japan which showed similar correlations to those that appeared in the animal studies; i.e., death rate from stroke in the population from the mountain village was nearly twice as high as the rate in the fishing village. Sodium intake was similar in both villages, although diastolic blood pressures were slightly higher in the mountain village. Results from this human study showed similar correlations to those observed in the animal experiments.

- 9) "International Network of Food Data Systems (INFOODS)," was presented by Vernon R. Young, Ph.D., Professor of Nutritional Biochemistry, Massachusetts Institute of Technology, at the August 2, 1984 NCC meeting. A summary of his presentation is given below.



Increasing interest in and concern for the relationships between diet, food habits, and degenerative diseases including coronary heart disease, diabetes, hypertension, stroke and cancers, has stimulated the current interest in detailed chemical data on foods. Data on the nutrient and nonnutrient composition of foods, beverages, and their ingredients contribute to a variety of research and service activities. For example, these data could be used for the establishment of safe and adequate intakes of essential nutrients and nonnutrient components of foods, for epidemiological studies on the relationship between diet and degenerative diseases, and for the formulation of national food and nutrition policies and programs.

At present, numerous food composition data bases exist; however, much of the data are of varying reliability, out-of-date, and incomplete in terms of either items listed or components described. These data bases also tend to be incompatible with one another and are often difficult to access. Problems with data bases are becoming more acute as new foods and new methods of production and storage are continually being developed and as international food trade expands.

Another facet of the problem is that while most of the information on the components of food is currently disseminated in the conventional, printed-page format, modern information processing technology is increasingly being used by those involved in all areas of the production and use of food composition data. The problems that arise from nonstandardized, nonevaluated data collection, storage, and dissemination affect all those in the scientific and technical community involved with food composition data.

An international planning conference on the topic of "The International Network of Food Data Systems in Foods" was held January 30 to February 5, 1983 in Bellagio, Italy. This conference was sponsored by the Food, Nutrition, and Poverty Subprogramme of the United Nations University and supported by various U.S. Government agencies, private foundations, and the food industry. Representatives from the Food and Agriculture Organization of the U.N., the World Health Organization, the International Union of Nutritional Sciences, and the International Union of Food Science and Technology participated in the discussions. The participants recommended that an international effort should be initiated to promote international participation and cooperation in the acquisition and dissemination of complete and accurate data on the composition of foods, beverages, and their ingredients in forms appropriate to meet the needs of the users. The establishment of an International Food Composition system would enhance the quality, quantity, and accessibility of the nutrient and nonnutrient data. This system will give reliable representative data for indigenous foods, and whenever possible, reflect the effect of growing conditions and treatments before consumption. Thus, comprehensive studies of nutrients or other components in foodstuffs including contaminants, toxic substances, and nonnutritive chemicals could be undertaken.

In order to develop such a system a number of steps will be taken, which will be carried out with the support of NCI, NHLBI, and FDA,



over 4 years. Particular attention will be paid to data quality, including recommendations and guidelines for methods of analysis and reporting of data. The first step involves the establishment of an international committee to meet and establish user needs and requirements by evaluating the types of data searches most commonly utilized and establishing the scope of detail needed in regard to food items, properties of food, and factors that influence these properties. An International Committee will also evaluate the present practices of food analysis, determine the problems, and recommend valid and acceptable methods for the sampling of foods for analysis, preparing samples and analytical methods for various nutrients in a variety of foodstuffs. Subsequently, guidelines will be established for the gathering of data for inclusion in the international food data system. The content and format of existing data systems that deal with nutrients, contaminants, additives, or other numerical data will be evaluated in terms of how they can contribute to an international data system. An international standardized documentation and nomenclature language will be established that would be internationally acceptable, flexible, and responsive to the needs of modern computer technology for data entry, summarization and/or statistical manipulations as well as user-responsive retrievals. A standard retrieval system for small machine, i.e., personal computer, use will be designed as a product of this initiative. The nomenclature will unambiguously identify food items, its parts, processes, and other quality characteristics; identify all results of the analyses as well as conditions, such as environmental, that may have affected these properties. This documentation will be published as a handbook. The content of the data base for the system will be determined by the details required about food by the users, the quality and quantity of data required and available, and the scheme of unambiguous identification of foods and substance, and factors affecting them. The system will allow for easy access from existing systems into the proposed system.

Dr. Young concluded that international liaison committees will be established. These committees will serve in an advisory capacity, promote widespread knowledge of the food composition data system and promote cooperation in the use of the system and exchange of data. The participation of international organizations is expected to include the Food and Agriculture Organization of the United Nations, and World Health Organization (WHO), international scientific unions such as the International Union of Nutritional Science, the International Union of Food Science and Technology, and the International Union of Pure and Applied Chemists, as well as country governments, universities, and food industry.

- 10) "International Nutrition Research Programs of NICHD and NCI," was presented by Gilman Grave, M.D., Chief, Section on Nutrition and Endocrinology, NICHD, and William DeWys, M.D., Associate Director of Prevention, DCPC, NCI, at the September 6, 1984 NCC meeting. A summary of their presentation is given below.

Dr. Grave reported that in FY 1984, NICHD expended approximately \$5,000,000 or 2 percent of the total NICHD budget on all their inter-

national projects combined. These projects were primarily related to demography and population control. The 19 international nutrition projects accounted for only 0.5 percent of the total NICHD budget (6 percent of the NICHD nutrition program) and focused primarily on the problem of maldistribution of the world's food resources and the effects of undernutrition on child development and socialization. On a global basis, it is estimated that 450 million people, primarily infants and children, are threatened with starvation. The international nutrition research program of NICHD is devoted to determining the best possible utilization of the world's food supply and to ascertaining the kinds of locally available nutritional support that will permit the full potential of human development.

Dr. Grave summarized the findings of two major international nutrition projects: 1) A 13-year study of the effects of mild to moderate malnutrition on child development carried out in four rural villages in Guatemala, and 2) a project to investigate the relationships among commercial agriculture, migratory wage labor, family land availability, cash income, and health and nutritional status of young children in a rural area of Coast Province, Kenya.

The study of a group of villages in rural Guatemala included all children under 7 years of age and all pregnant and lactating women from February 1969 to February 1973. Thus, the sample consisted of 1,444 children born between January 1962 and February 1973. Only one cohort of children was observed from birth to 7 years, the 180 children born between February 1969 and March 1970. Data on growth, morbidity, home diet, family socioeconomic status, and cognitive development were collected regularly on all children until March 1977. Children in two villages received Atole, a high protein (6.4 grams/deciliter) and high calorie beverage (91 kilocalories/deciliter), while counterparts in two control villages received Fresco, a beverage with no protein and fewer calories (37 kilocalories/deciliter).

The following findings were generated by the study:

- o The social environment in which malnutrition occurred had powerful effects on cognitive development. Logistical difficulties in estimating the separate contributions of the intertwined variables were also apparent.
- o Both Atole and Fresco were consumed in large quantities by the 740 pregnant women who participated in the study. This supplementation appeared to cause significant increases in their babies' birth weight; these increases were attributable to increased caloric ingestion, since the dose-response of caloric ingestion and birth weight was similar for both Atole and Fresco.
- o Atole ingestion was associated with increased physical growth for children in the Atole villages, whereas Fresco ingestion was not associated with increased growth for children in the control villages.

- o Morbidity data collected after June 1970 on children 7 years old or less and on mothers during pregnancy and lactation showed the morbidity of study children to be negatively related to physical growth in all periods from birth to 7 years of age. Quality control procedures included concurrent validation of symptoms reported in 10 percent of the sample by a morbidity survey supervisor and a physician.
- o Biochemical measurements on the children demonstrated that the nutritional supplementation with Atole improved nutritional status. Atole intake was associated with a high ratio of urea/creatinine excretion thereby indicating an increase of protein availability. Fresco intake, however, was associated with a low ratio of urea/creatinine excretion, suggesting that the provision of calories alone resulted in protein sparing.
- o Nutritional supplementation during infancy was positively and significantly associated with improved developmental test scores. Preschool psychological test performance was found to be superior in the Atole villages and among children with higher levels of total nutrient intake within Atole villages.
- o Although psychological test performance is strongly conditioned by social environmental factors, nutritional factors were shown to play an independent role in cognitive development. Performance on a wide range of psychological tests was affected by mild-to-moderate malnutrition. Thus, the hypothesis that chronic mild-to-moderate protein-energy-malnutrition affects mental development was confirmed.
- o In a subset of the children, investigators found improved socialization skills in supplemented children.

The study in Kenya included four communities: Msidunyi--an area of subsistence agriculture severely impacted by absentee migratory wage labor and where commercial production is insignificant as a source of household income; Iparenyi--a lush highland area where coffee and vegetable production is the principal source of household cash income; Bondeni--a poor dry area of traditional subsistence agriculture in the lowlands, targeted for developmental assistance in cotton, legume, and grain production by USAID; and Mkonge estate--a sisal estate in the highlands inhabited by laborers who work for wages and have little or no opportunity to produce food for their own consumption. Measures of the nutritional status of 700 children living in these communities included weight, recumbent length, mid-upper arm circumference, and triceps skinfolds with assessments done at different seasons of the year when food availability and requirements for work differed.

The three hypotheses tested in the study and their conclusions are presented below:

Hypothesis 1. In general, cash cropping has negative effects on nutritional status; i.e., the nutritional status is worse in



villages heavily involved in commercial agriculture than in less commercialized villages.

Conclusion. The study revealed that the commercial production of coffee and vegetables is associated with a better nutritional status of children. Farmers in Iparenyi turned over only a portion of their land to growing coffee and vegetables, and produced a substantial portion of their own food. These people did not depend on the vagaries of crop sales as a means of obtaining cash to purchase food for home consumption.

Hypothesis 2. Family land availability is positively correlated with nutritional status. The more land a family has available through ownership, renting, or borrowing, the better a family's nutritional status will be.

Conclusion. Landless laborers working on sisal estates had children with a better nutritional status than those in agricultural communities (except Iparenyi, where commercial agriculture is significant) since the bulk of household income is spent on food purchases. Estate workers consume more animal protein and more high-calorie snacks than residents of sisal traditional subsistence farming communities. Many estate workers' children purchase a midday meal instead of going without or foraging for wild fruits. Their families have a breakfast meal in the morning instead of the hot, sweet tea consumed in traditional farming communities. Satisfactory wage rates and low local food prices work in favor of landless households on the sisal estate with regard to nutritional outcomes.

Hypothesis 3. Migratory wage labor has generally negative effects on the nutritional status of both wage laborers who leave and their families who remain behind.

Conclusion. This study revealed that adult members of households with the best nourished children devoted 40 percent of their time to employment off the farm, versus 15 percent for members of households with the worst nourished children. Analysis of labor-time allocation shows that better nutrition in children under 5 years of age is attended by a greater emphasis on off-farm employment in the agricultural communities. Adults from households whose children are the worst nourished spend a great deal of time on other activities such as food preparation and cooking, water collection, social and ritual activities, etc. This is partially due to the degree of unemployment and underemployment. These results suggest that increased opportunities for rural off-farm employment may directly affect nutritional status.

Dr. Grave concluded that, under some circumstances in East Africa, commercialization of agriculture and involvement in wage labor are associated with substantial nutritional benefits. Some households achieve these benefits through commercial production alone, others through labor sales alone, while others do both. Those households with substantial cash income generated via sales of crops or labor



generally outproduce other households with respect to major staples of maize and beans. The cash allows the use of improved planting materials and can finance local laborers to clear, plant, and weed crops. The percent of children who were both stunted and wasted was 21 percent in Msidunyi but only 5 percent on the sisal estate.

Dr. DeWys presented an overview of 20 international nutrition research projects supported by NCI that included epidemiological studies, laboratory research projects, prevention intervention trials, and cancer treatment projects.

The epidemiological studies cover the following research areas: development and implementation of an International Food Composition Data System that will facilitate studies of nutrient intake around the world (see presentation by Dr. Young, page 298 ; evaluation of the carcinogenic risk to humans of chemicals and the publication of this information in an IARC monograph; determination of the degree of exposure of staple foods to high levels of toxic substances (pesticides and chemical fertilizers) in Puerto Rico and its relationship to exposing populations to potential carcinogens; evaluation of dietary selenium as a cancer risk factor in China; determination of the role of diet in the etiology of cervical cancer in South America; testing of the hypothesis that populations at high risk of gastric carcinoma in Colombia consume diets low in protein, fat, and calories and high in irritants and abrasives such as salt, grains, and fried foods; examining the association of various risk factors, including diet, for colorectal cancer in Chinese and Chinese Americans; evaluation of the relationship between serum retinol, tocopherol, selenium, and zinc and the subsequent development of lung and stomach cancers among atomic bomb survivors in Japan; assessment of dietary intake of meat, fiber, fat, retinol, and carotene and its association with increased risk of colorectal cancer in atomic bomb survivors; and assessment of dietary intake of iodine, goitrogens, retinol, and carotene in a case control study of thyroid cancer in atomic bomb survivors.

Laboratory studies under way in Canada and England are investigating the types of perturbations caused by an imbalance of nucleotides and the effects of orotic acid, thymine, and thymidine in terms of promoting liver carcinogenesis; the effects of relatively prolonged exposure of hepatocytes to hepatocarcinogens that may constitute a source of natural exposure from the diet and/or contents of the gastrointestinal tract; and the effects of cancer promoters such as saccharine and tryptophan and antipromoters such as retinoids in previously initiated carcinogenesis of rat bladder.

The five cancer prevention intervention trials include studies in China on the role of micronutrients in esophageal dysplasia and lung and stomach cancers; studies in Finland on the correlation of beta-carotene and vitamin E with the incidence of lung cancer in heavy smokers; studies in Italy and England on the role of 4-hydroxyphenyl-retinamide in the prevention of breast cancer and bladder cancer respectively; and studies in Tanzania on the prevention of skin cancer with beta-carotene.

The two studies on cancer treatment under way in Canada are investigating the nutritional status of patients with advancing malignancy and the influence of nutritional status on the viability and death of cells in suspension and in spheroids (specifically, glucose, pyruvate, lactate, pH, oxygen tension, and glutamine). The latter study is also investigating the interactions between nutrients and metabolites that lead to cell death in tumors. The rationale behind this study is the observation that nutritionally deprived cells in spheroids and tumors appear to be spared by some anticancer drugs because of limited drug distribution from blood vessels to the surrounding media.

Dr. DeWys concluded that the results of this research will indeed provide more insight on the role of diet and specific nutrients in the etiology, prevention, and treatment of certain cancers.



## **APPENDIX J**

### **GUIDELINES FOR REVIEW OF NIH NUTRITION PUBLICATIONS FOR THE PUBLIC**





## GUIDELINES FOR REVIEW OF NIH NUTRITION PUBLICATIONS FOR THE PUBLIC

The guidelines used by the Subcommittee in their review of the nutrition pamphlets destined for the public are presented below:

### 1. General

- a. Each publication is reviewed for scientific accuracy and consistency with related publications so that "mixed messages" are avoided.
- b. Each publication should serve a specific public need and provide useful information which the public can put into practice.
- c. Publications intended for the general public should not be self-serving of the Institute.
- d. Inconsistencies should be avoided by; 1) clearing the publication with appropriate Institutes, 2) comparing the publication with other similar publications, and 3) clearing the publication with the MCC.
- e. All publications should be dated and the pages numbered.
- f. Publications should be reviewed once a year for their usefulness and controversial subject areas which may have arisen since their development, e.g., saccharin, intestinal bypass surgery.
- g. Audience should be identified within the publication.
- h. If the publication contains the sample diets or menus, blank space should be provided for tailoring the diet according to the prescription.
- i. Brand names of foods should be avoided.

### 2. Titles

- a. Titles should be appealing
- b. Titles should be sufficiently informative to make GPO listing meaningful.

### 3. Content

- a. Style of writing should take into account the heterogeneity within the American population; content and reading levels should be appropriate to audiences differing in educational level, age, sex, and ethnicity.
- b. Low income and ethnic differences should be considered from the standpoint of content (ethnic food preferences and taboos, low cost foods, meatless meals).
- c. Scientific terms should be avoided or defined, avoiding technical detail.



APPENDIX K

LEGISLATIVE AUTHORITY OF NIH FOR HUMAN NUTRITION





## LEGISLATIVE AUTHORITY OF NIH FOR HUMAN NUTRITION RESEARCH

Two Institutes have specific mandates to conduct nutrition research at the NIH. Those mandates are as follows (references to PHS Act):

NCI: Section 407(b)(4)--"Collect, analyze, and disseminate information (including information respecting nutrition programs for cancer patients and the relationship between nutrition and cancer) useful in the prevention, diagnosis, and treatment of cancer, including..."

NHLBI: Section 413(a)(1)--"investigation into the epidemiology, etiology, and prevention of all forms and aspects of heart, blood vessel, lung, and blood diseases, including investigations into the social, environmental, behavioral, nutritional, biological, and genetic determinants and influences..."

Section 413(d)--"There shall be in the Institute an Assistant Director for Prevention, Education and Control...In the conduct of such a program, special emphasis shall be placed upon dissemination of information regarding diet, exercise, stress, cigarette smoking, weight control..."

Other Institutes that conduct and support nutrition research do so under much broader authority. Each conducts research programs in the "diagnosis, prevention, and treatment" of specific diseases and life processes within their areas of responsibility. Those authorities are as follows:

General authority	Section 301
International cooperation authority	Section 307
Training authority	Section 472(a)(1)(a)
NCI	Section 402(a)
NHLBI	Section 412(1)
NIDR	Section 422(a)
NIADDK	Section 434(c)
	Section 434(a)
	Section 439(a)
NICHD	Section 441(a)
NIGMS	Section 442
NIA	Section 464
Other Institutes	Section 431(b)

NCI LEGISLATIVE AUTHORITY FOR NUTRITION INFORMATION  
AND EDUCATION PROGRAMS

The specific mandates of the NCI for nutrition information and education programs are contained in Section 407(b)(4) of Public Law 92-218, "The National Cancer Act of 1971," as amended in Public Law 93-352, "Title I - Extension of Cancer Program":

P.L. 92-218, Section 407(b)(4): "Collect, analyze, and disseminate all data useful in the prevention, diagnosis, and treatment of cancer, including the establishment of an international cancer research data bank to collect, catalog, store, and disseminate insofar as feasible the results of cancer research undertaken in any country for the use of any person involved in cancer research in any country."

P.L. 93-352, Section 103: "Section 407(b)(4) of the Public Health Service Act is amended by striking out 'all data' and inserting in lieu thereof 'information (including information respecting nutrition programs for cancer patients and the relationship between nutrition and cancer).'

NHLBI LEGISLATIVE AUTHORITY FOR NUTRITION INFORMATION  
AND EDUCATION PROGRAMS

The specific mandates of the NHLBI for nutrition information and education programs can be found in Section 413 of the Public Health Service Act, March 1977. This Section indicates the general plan for the Institute to expand, intensify, and coordinate the Institute's activities in the areas of heart, blood vessel, lung, and blood diseases and blood resources. To implement this mandate, Section 413(a)(1) states:

"Investigation into the epidemiology, etiology, and prevention of all forms and aspects of heart, blood vessel, lung, and blood diseases, including investigations into the social, environmental behavioral, nutritional, biological, and genetic determinants and influences involved in the epidemiology, etiology, and prevention of such diseases."

Section 413(d) states the following:

"There shall be in the Institute an Assistant Director for Prevention, Education, and Control who shall be appointed by the Director of the Institute. The Director of the Institute, acting through the Assistant Director for Prevention, Education, and Control, shall conduct a program to provide the public and the health professions with health information with regard to cardiovascular and blood and pulmonary diseases and blood resources. In the conduct of such program, special emphasis shall be placed upon dissemination of information regarding diet, exercise, stress, hypertension, cigarette smoking, weight control, and other factors affecting the prevention of arteriosclerosis and other cardiovascular diseases and of pulmonary and blood diseases."

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**DISCRIMINATION PROHIBITED:** Under provisions of applicable public laws enacted by Congress since 1964, no person in the United States shall, on the grounds of race, color, national origin, handicap, or age, be excluded from participation in, be denied the benefits of, or be subjected to discrimination under any program or activity (or, on the basis of sex, with respect to any education program or activity) receiving Federal assistance. In addition, Executive Order 11141 prohibits discrimination on the basis of age by contractors or subcontractors in the performance of Federal contracts, and Executive Order 11246 states that no federally funded contractor may discriminate against any employee or applicant for employment because of race, color, religion, sex, or national origin. Therefore, the Nutrition Coordinating Committee must be operated in compliance with these laws and Executive Orders.



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